

**PTAC meeting held 5 & 6 August 2010**

**and**

**PTAC email meeting held 26 August to 6 September 2010**

**(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) in order to protect the privacy of natural persons (section 9(2)(a)).

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## 1 Minutes of PTAC meeting held May 2010

- 1.1 The Committee reviewed the minutes of the PTAC meeting held on 6 & 7 May 2010 and made the following minor amendment:
  - 1.1.1 Metronidazole vaginal gel – paragraph 8.7: replace: “Members considered that metronidazole was not more effective than oral metronidazole” with “Members considered that vaginal metronidazole was not more effective than oral metronidazole”.

## 2 Multiple sclerosis treatments

### Application

- 2.1 The Committee considered submissions from [ withheld under s9(2)(a) of the OIA ] (consultant to previous applicants Bayer NZ Ltd, Sanofi-Aventis NZ and Biogen Idec NZ Ltd), members of the Neurological Subcommittee of PTAC and members of the Multiple Sclerosis Treatment Assessment Committee (MSTAC), and reviewed information provided by PHARMAC staff, in relation to previous applications by various parties to widen funded access to the multiple sclerosis (MS) treatments beta-interferon (interferon beta-1-alpha [Avonex] and interferon beta-1-beta [Betaferon]) and glatiramer acetate (Copaxone).
- 2.2 The Committee noted that the main issues for discussion related to inputs into PHARMAC’s cost-utility analysis (CUA) and the three proposed changes to the access criteria, broadly summarised as follows:
  - to allow treatment with a second class of MS medication after failure of treatment (as defined by current criteria) with the first class of treatment (referred to as “treatment switching”);
  - to amend the entry criteria to allow earlier treatment; and
  - to amend or remove the exit criteria to allow longer treatment.

### Recommendation

- 2.3 The Committee reiterated its previous **recommendation** (made in November 2008) that the criteria for access to MS treatments be amended to permit treatment switching in

patients with a stable or increasing relapse rate over 12 months of treatment (compared with the relapse rate prior to starting treatment), provided that no other exit criteria are met. The Committee assigned a medium priority rating to this recommendation.

- 2.4 The Committee also reiterated its previous **recommendation** to amend (not remove) the exit criteria for MS treatments as previously described (in November 2008). However, the Committee altered the priority of this recommendation from low (as prioritised in February 2010) to medium (as originally prioritised in November 2008).
- 2.5 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.*
- 2.6 The Committee **deferred** re-consideration of its previous recommendation to decline all applications to amend the entry criteria for funded access to MS treatments pending an updated CUA to be performed by PHARMAC staff for review by the Committee.

## Discussion

### *Treatment switching*

- 2.7 The Committee noted the support from MSTAC and members of the Neurological Subcommittee regarding the proposed changes to the access criteria to allow treatment switching.
- 2.8 The Committee considered that there was no new evidence presented in relation to this proposal and that there did not appear to be any compelling reason to change its previous recommendation to permit treatment switching with a medium priority.

### *Amending the exit criteria*

- 2.9 The Committee noted the support from MSTAC and members of the Neurological Subcommittee regarding relaxing of the exit criteria.
- 2.10 The Committee noted that it had previously recommended that the exit criteria be amended and had (in February 2010) changed the priority of this recommendation from medium (in November 2008) to low, partly because of newer evidence, in particular from the UK MS Risk-Sharing Scheme (Boggild et al. BMJ 2009;339:b4677), suggesting that MS treatments were less effective in a 'real life' setting than had been seen in the clinical trials.
- 2.11 The Committee noted MSTAC's view that the outcomes reported from the UK MS Risk-Sharing Scheme are intrinsically limited and should not be relied upon as evidence of poor effectiveness. MSTAC had considered that if the data were not adjusted to remove the effect for patients who reported improvement from treatment, the outcomes overall may be better than reported.

- 2.12 The Committee noted that the Boggild 2009 paper had itself highlighted many of the issues raised by MSTAC and that many of these issues were inherent in other cohort studies. The Committee considered that, taken as a whole, the cohort studies – including the UK MS Risk-Sharing Scheme – comprised a large dataset which, in essence, indicated that the treatments were potentially less effective in clinical practice than might be expected based on randomised clinical trial results. The Committee noted that the adjustments to the UK MS Risk-Sharing Scheme data, to remove the effect of patients who reported improvement associated with treatment, had been made because the authors considered this was necessary to correctly compare with data from historical untreated controls that had removed improvements in disability.
- 2.13 The Committee noted that the degree of functional impairment associated with an increase in one Expanded Disability Status Scale (EDSS) point varied considerably at different parts of the scale, and that at lower EDSS scores greater uncertainty arose with incremental changes in EDSS scores. The Committee considered that the instability of EDSS changes at lower baseline EDSS scores was due to the greater effects from EDSS states aggregating disparate functional health states and the potential for greater variation in test/retest (day-to-day) and inter-rater reliability. The Committee also noted that longer follow-up periods to confirm persistent EDSS deterioration when still recovering from a relapse were particularly important for lower EDSS states, given the greater variability. The Committee considered that such uncertainty strengthened the case for it recommending the relaxation of the exit criteria by increasing the time needed to confirm progression and for patients with lower baseline EDSS scores having longer disease progression times.

*Amending the entry criteria*

- 2.14 The Committee noted the support from MSTAC and members of the Neurological Subcommittee for amending the entry criteria to allow earlier access to funded treatment.
- 2.15 The Committee noted that it had previously recommended that all the applications to amend the entry criteria be declined, on the basis of lack of evidence and poor cost-effectiveness.
- 2.16 The Committee reiterated its view that there was no high-quality evidence (ie, long-term randomised controlled trials or good quality meta-analyses) directly supporting a reduction in long-term disability from early treatment with beta-interferon or glatiramer, noting that there was only relatively short follow-up of the blinded phase in the available randomised controlled trials. The Committee noted that the highest quality evidence refers to two-year outcomes and disability was not an outcome measure.
- 2.17 The Committee considered that the evidence supporting long-term benefits of early treatment with beta-interferon or glatiramer is of relatively low quality and for a limited time-frame (3–5 years) after commencing treatment. The Committee considered that the risk of bias in the available studies is moderately high because of unmasked assessment of outcomes and non-randomised treatment allocation. Further, the extension studies of the randomised controlled trials (reported as cohort studies) had high drop-out rates which could bias estimates of effectiveness.
- 2.18 The Committee considered that there was insufficient evidence available to amend its previous recommendation regarding the entry criteria. However, the Committee noted

that it would be prepared to re-consider this recommendation following review of an updated CUA to be performed by PHARMAC staff.

- 2.19 The Committee noted that fresh evidence may emerge that indicates the clinical circumstances under which early treatment reduces inflammation and relapses more than later treatment, and that these effects may be shown to be associated with comparatively larger reductions in longer-term disabilities. The Committee considered that if early treatment under such circumstances was the option preferred by MSTAC and the Neurological Subcommittee, then the Committee would consider supporting such early treatment. Such support by the Committee would be fully contingent on the supporting evidence being of good quality; MSTAC and the Neurological Subcommittee being able to identify suitable entry criteria; treatments being funded within the existing budget; and early treatment being cost-effective relative to later treatment. The Committee noted that the budgetary requirement might necessitate commensurate tightening of the current exit criteria.

*Assumptions and inputs recommended for use in the updated CUA*

- 2.20 The Committee noted that [ withheld under s9(2)(a) of the OIA ] submission contained a number of assertions and comments relating to the economic modelling of MS treatments, including comments regarding the efficacy of MS treatments in early EDSS states and evidence for improvement of EDSS from treatment in early stage disease. The Committee took these comments, and those of PHARMAC staff, the Neurological Subcommittee and MSTAC, into consideration when making recommendations regarding inputs to be used in the CUA to be completed by PHARMAC staff.
- 2.21 The Committee noted that PHARMAC staff will continue to work with members of the Committee, MSTAC and the Neurological Subcommittee to further substantiate specific clinical inputs in the updated CUA, prior to review by the Committee.

*Comment on clinical studies*

- 2.22 The Committee noted that part of the difficulty in making informed recommendations in relation to access criteria for funding of beta-interferon and glatiramer was the lack of good quality clinical trial data, and that it was reasonably unlikely that such data would become available in the future, given that clinical trials were currently focussing on new treatments such as alemtuzumab, natalizumab and fingolimod.
- 2.23 The Committee noted that it was, however, possible to gain some insight into the effectiveness of beta-interferon and glatiramer where these have been used in the control arms in studies of the newer treatments. For example, as the Committee had previously noted, the results of two double-blind, double dummy randomised clinical trials of fingolimod in relapsing-remitting MS (TRANSFORMS: Cohen et al. New Engl J Med 2010;362:402-15; FREEDOMS: Kappos et al. New Engl J Med 2010;362:387-401), both with over 1,000 participants, appeared to show little differences between the beta-interferon arm of the TRANSFORMS study and the placebo arm of the FREEDOMS study for both their post-treatment annualised relapse rates and the change between pre- and post-treatment annualised relapse rates.
- 2.24 The Committee also noted that the beta-interferon arm in the TRANSFORMS study had a higher relapse rate than in the meta-analysis of previous RCTs of beta-interferon (Rice

et al, Cochrane Database of Systematic Reviews 2001:Issue 4:CD002002), and considered that this raised the possibility of bias in previous RCTs and cohort studies, which may have, therefore, overestimated the effectiveness of beta-interferon and glatiramer in MS. The Committee also considered that the apparent higher comparative relapse rate in the TRANSFORMS beta-interferon arm was consistent with the results of the analysis of the UK MS Risk Sharing Scheme (Boggild 2009), where treatment appeared worse in this cohort than in the RCTs of beta-interferon. The Committee considered that if the beta-interferon arm of the TRANSFORMS fingolimod trial had reported an unbiased estimate of relapse rates, then its higher relapse rate than in the beta-interferon trials would support a more pessimistic estimate of the overall effectiveness of beta-interferon in MS. The Committee considered that, to this extent, the estimate of the relapse rates from the beta-interferon arm of the TRANSFORMS fingolimod trial was level 2++ evidence (high quality cohort data with a very low risk of confounding, bias or chance) and considered this to be a higher grade of evidence than nearly all of the cohort studies of beta-interferon. The Committee considered that although the fingolimod trials were limited by short follow-up time, in relation to the length of illness, the previous cohort studies were no less limited with regard to duration.

### **3 Pipobroman for polycythemia rubra vera and essential thrombocythemia**

#### **Application**

- 3.1 The Committee reviewed an application from a clinician for the listing of pipobroman on the Pharmaceutical Schedule for the treatment of patients with polycythaemia rubra vera (PV) or essential thrombocythaemia (ET) whose disease had not respond to hydroxyurea (HU) or for patients intolerant to HU treatment. Members noted that the application was prompted by a review of EC applications by the Cancer Treatments Subcommittee (CaTSoP) at its November 2009 meeting.

#### **Recommendation**

- 3.2 The Committee **recommended** that pipobroman should be funded on the Pharmaceutical Schedule for the treatment of patients with ET or PV whose disease was refractory to HU or for patients intolerant to HU treatment. The Committee gave this recommendation a medium priority.
- 3.3 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 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**

- 3.4 The Committee noted that PV is a rare chronic myeloproliferative disease, almost always associated with a JAK 2 (a protein tyrosine kinase) mutation, characterised by a clonal proliferation of red blood cells. Members considered that left untreated the median survival of patients with PV is approximately 6-18 months with the main causes of death being thrombotic events and haemorrhage in the short term and transformation to Acute Myeloid Leukaemia (AML) and myelofibrosis in the longer term.
- 3.5 The Committee noted that ET is a rare chronic myeloproliferative disease characterised by a clonal proliferation of platelets, leading to platelet dysfunction and increased risk of thromboembolism. Members noted that JAK 2 mutation was present in approximately 50% of patients with ET and that in general transformation to AML and myelofibrosis in patients with ET is rare, but more common in patients with a JAK 2 mutation.
- 3.6 The Committee considered that the goal of PV and ET treatment was to prevent vascular events and minimise the risk of disease transformation to AML. Members noted that current treatment options for PV and ET patients included phlebotomy and low dose aspirin with cytoreductive therapy used in older patients (> 60 years) or those at higher risk (previous vascular events). Members considered that the current first line cytoreductive treatment of choice was hydroxyurea (HU), with most patients receiving anagrelide as second line treatment if their disease failed to respond to HU, or if they were intolerant of HU. Members noted that a number of other treatments of PV/ET were currently being evaluated in clinical trials including pegylated interferon, imatinib and JAK 2 inhibitors.
- 3.7 The Committee noted that pipobroman is a bromide derivative of piperazine. It is both an alkylating agent and a metabolic competitor of pyrimidine nucleotides inhibiting the activity of DNA/RNA polymerases. Members noted that the dose of pipobroman was variable, being dependent on an individuals' cell count and body weight.
- 3.8 The Committee noted that pipobroman is not approved by MedSafe and currently is not available from any suppliers in New Zealand. Members further noted that pipobroman is not listed in the British National Formulary (BNF) but is registered in some European countries, in particular Italy and France. Members noted that although some supplies of pipobroman (Vercyte, Abbott France) had previously been imported into New Zealand ongoing supply of pipobroman was uncertain.
- 3.9 The Committee reviewed evidence for the use of pipobroman in patients with PV or ET from a number of studies. Members considered the evidence provided to be of poor to moderate quality comprising mainly single arm studies in treatment-naïve patients. Members noted that there is no evidence for the use of pipobroman in treatment experienced PV or ET patients, nor are there any comparative trials comparing pipobroman and anagrelide.
- 3.10 The Committee reviewed evidence from two comparative studies, one comparing treatment with HU and pipobroman in treatment-naïve PV patients (Najain and Rain 1997) and another comparing HU and anagrelide in treatment-naïve ET patients (Harrison et al 2005).
- 3.11 The Committee considered that pipobroman appears to be as effective as HU in treatment-naïve patients. Members considered that HU and anagrelide had similar efficacy in terms of haematological response in treatment-naïve ET patients but

anagrelide was less protective for thrombotic or haemorrhagic events. Members considered that overall the evidence suggested that pipobroman is effective at achieving a haematological response in treatment naïve patients with PV or ET and it is reasonably well tolerated with gastrointestinal adverse events being the main problem.

- 3.12 The Committee noted that pipobroman, HU and anagrelide were all associated to some extent with an increased risk of AML transformation, however, the magnitude of risk for pipobroman compared with other treatments was not clear. Members considered that AML transformation is part of the natural progression of myeloproliferative diseases such as PV and ET and in treating these diseases it was important to balance the short term risk of vascular events, if left untreated versus treatment with cytoreductive agents which increase life expectancy by reducing the risk of vascular events but increase the risk of secondary leukaemias.
- 3.13 The Committee noted that at the prices quoted in the submission pipobroman appeared to be cheaper than anagrelide but more expensive than HU. Members therefore considered it to be reasonable to consider that pipobroman be funded for the second line treatment of patients who would otherwise currently be treated with anagrelide. Members considered that there would be approximately 20 such patients per year.
- 3.14 The Committee noted that because it was not approved by MedSafe if pipobroman was listed on the Pharmaceutical Schedule clinicians would be required to prescribe it in accordance with the provisions of Section 29 of the Medicines Act. Members considered that given the absence of a supplier for pipobroman in New Zealand PHARMAC would be unable to secure ongoing supply or price.

## 4 Azacitidine (Vidaza) for myelodysplastic syndromes

- 4.1 The Committee reviewed an application from Celgene Pty Ltd for the listing of azacitidine (Vidaza) on the Pharmaceutical Schedule for the treatment of patients with intermediate-2 or high risk Myelodysplastic Syndromes (MDS), Chronic Myelomonocytic Leukaemia (CMML) or Acute Myeloid Leukaemia (AML).

### Recommendation

- 4.2 The Committee **recommended** that azacitidine should be funded on the Pharmaceutical Schedule for the treatment of patients with intermediate-2 or high risk MDS, CMML or MDS-associated AML. The Committee gave this recommendation a low priority.
- 4.3 The Committee further **recommended** that the application be referred to CaTSoP for further advice regarding the proportion of patients receiving current treatment options for MDS patients in New Zealand, the Special Authority criteria for azacitidine, the number of patients likely to be treated with azacitidine, and inputs for the budget impact and cost effectiveness analyses.
- 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 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, 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**

- 4.5 The Committee noted that the term myelodysplastic syndrome (MDS) encompasses a heterogeneous group of closely related clonal hematopoietic disorders that principally affects older patients. Members considered that MDS was incurable and that approximately 30% of patients with MDS would progress to Acute Myeloid Leukaemia (AML). Members noted that approximately 300 patients per year would be diagnosed with MDS in New Zealand. However, members considered that currently MDS was under reported in New Zealand therefore in reality many more patients could be treated.
- 4.6 The Committee considered that current treatment options for MDS patients were based on IPSS prognostic staging which was based on percentage of bone marrow blasts, karyotype and cytopenias. Without treatment patients with low risk would be expected to survive approximately six years, whereas those with high risk features would be expected to progress to AML and survive only around one year. Members considered that approximately one third of patients would present with IPSS INT-2/high risk disease at diagnosis.
- 4.7 The Committee noted that the goal of MDS treatment was to control symptoms, improve quality of life, improve overall survival, and decrease progression to AML. Members noted that there is generally a watch and wait approach in low risk patients who are asymptomatic, however symptomatic IPSS INT-2/high risk patients would receive best supportive care (BSC) with or without active chemotherapy and/or stem cell transplant. Members considered that BSC included transfusions, and in some cases iron chelation. Member's considered that there were resource constraints with stem cell transplantation and its use would also be limited given the age and performance status of most individuals with MDS.
- 4.8 The Committee noted that azacitidine is a nucleoside analogue, its effect being mediated by hypomethylation of DNA leading to apoptosis of rapidly dividing cells, including haematopoietic cancer cells. Members further noted that azacitidine is a teratogen. Members noted that the recommended starting dose for azacitidine is 75 mg/m<sup>2</sup> given subcutaneously, daily for seven days, with treatment cycles repeated every 28 days and continued as long as the patient continues to benefit or until disease progression.
- 4.9 The Committee reviewed evidence from two key clinical trials comparing azacitidine with conventional care (including BSC) in patients with MDS. Members considered that the evidence was of moderate quality and strength.
- 4.10 The Committee noted that the first study (AZA-001, Fenaux et al 2009) was an open label randomised study of 358 patients comparing azacitidine plus BSC with planned conventional care (either BSC, low-dose cytarabine, or chemotherapy as selected by

investigators before randomisation). Members noted that this study enrolled patients with INT-2/high risk MDS or CMML, which was most representative of the population being requested for funding. However, the Committee noted that patients with prior-therapy related MDS were excluded from this study and members considered that these patients were an important group which may comprise a significant number of patients.

- 4.11 The Committee noted that after a median follow-up of 21 months 82 patients in the azacitidine group had died compared with 113 in the conventional care group. Median overall survival, the primary endpoint of the study was 24.5 months in the azacitidine group compared with 15 months in the conventional care group, a difference of 9.4 months (HR for overall survival was 0.58 (95% CI 0.43–0.77,  $p=0.0001$ ). Members noted that the survival benefit for azacitidine persisted across cytogenetic and IPSS score subgroups, and the time to AML transformation was longer. Members noted that although the rate of transfusions per year was lower in the azacitidine treated patients (10.6 per annum compared with 18.3 per annum), because these patients lived longer overall they received more transfusions. Members noted that azacitidine was associated with a higher incidence of grade 3/4 thrombocytopenia and neutropenia, with the incidence of these events being 2-fold higher than the BSC only treatment patients, but it was less than the low-dose cytarabine treatment patients and similar to that seen in the chemotherapy group.
- 4.12 The Committee noted that a report from the Unit of Public Health, Epidemiology and Biostatistics, University of Birmingham completed in July 2009, raises concerns about potential bias in the AZA-001 study due to loss to follow-up based on additional data supplied in confidence by the supplier. Members were concerned about the Birmingham group's view but were unclear as to what data this referred to and noted that the data provided in the supplier's application indicated that only one patient per arm was lost to follow-up. Members requested that PHARMAC staff follow-up with the supplier on this point.
- 4.13 The Committee noted that the second study (CALGB 9221, Silverman et al 2002) was an open label study in 191 patients comparing azacitidine with BSC alone; members considered this study to be less relevant to the application in that it enrolled MDS patients across all IPSS risk categories (only 46% of whom were INT-2/High risk). Members also noted that in this study patients on BSC whose disease was worsening were permitted to cross over to azacitidine.
- 4.14 The Committee noted that median time to AML transformation or death, the primary endpoint of the study, was 21 months for azacitidine treated patients compared with 12 months for BSC ( $P = 0.007$ ). For patients with high-risk MDS the median time to AML or death was 19 months for azacitidine patients compared with eight months for BSC ( $P = 0.004$ ). Members further noted that median survival was 20 months for patients treated with azacitidine compared with 14 months for BSC (53% of whom received azacitidine); however, this result was not statistically significant.
- 4.15 The Committee considered that overall the evidence demonstrated that azacitidine was associated with a survival advantage and was better tolerated than conventional treatments. However, members considered that azacitidine was essentially a palliative treatment and had relatively poor cost-effectiveness.

## 5 Docetaxel for early breast cancer

### Application

- 5.1 The Committee reviewed further information from the New Zealand Association of Breast Cancer Specialists – Breast Special Interest Group (BSIG) in response to its February 2010 minute regarding BSIG’s application for the widening of funded access to docetaxel for the adjuvant treatment of patients with early stage breast cancer.

### Recommendation

- 5.2 The Committee **recommended** that docetaxel should be funded on the Pharmaceutical Schedule for the adjuvant treatment of patients with early breast cancer in whom anthracycline treatment is contraindicated due to cardiomyopathy or high risk of cardiomyopathy. The Committee gave this recommendation a medium to high priority.
- 5.3 The Committee further **recommended** that the application be referred to CaTSoP for further advice regarding the Special Authority criteria for docetaxel, the number of patients likely to be treated with docetaxel, and inputs for the budget impact and cost effectiveness analyses.
- 5.4 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 products and related things; (iv) The clinical benefits and risks of pharmaceuticals; 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

- 5.5 The Committee considered that most of the points raised were not helpful to the comparison of docetaxel and paclitaxel. In particular the Committee considered that in order to correctly critically appraise the Sparano study it was appropriate to consider the data from all four arms of the Sparano study, including the three weekly paclitaxel arm. Members noted that the study was designed with the three weekly paclitaxel arm as the standard therapy arm, with the other three arms being compared against it. Members considered that it was not appropriate to selectively consider just the weekly paclitaxel and 3 weekly docetaxel arms of this study in isolation as suggested by BSIG.
- 5.6 The Committee noted that BSIG considered that it was not reasonable to support a treatment [paclitaxel] that results in neurological dysfunction [grade 3/4 peripheral neuropathy] in 4-8% of recipients. Members noted that in its February 2010 minute it commented that the incidence of paclitaxel-associated peripheral neuropathy was higher than docetaxel. However, members also noted that in the Sparano trial 4% of patients treated with 3 weekly docetaxel suffered from grade 3/4 peripheral neuropathy, and that these data were presented without any confidence limits. Moreover, members noted that in the Sparano study, the lowest incidence of neuropathic pain was seen in the weekly paclitaxel arm (<0.5%, grade 2), whereas the absolute incidence of grade 3/4 febrile neutropenia was 15% greater for 3 weekly docetaxel than for weekly paclitaxel (Sparano et al, NEJM 2007, Supplementary Appendix).

- 5.7 The Committee considered that docetaxel is still considerably more expensive than paclitaxel and there was little evidence provided regarding impact of neuropathy on patients' quality of life. Therefore, in the general early breast cancer population, it was unlikely that the health gains, and lower resource use from 3 weekly docetaxel outweighed its additional cost compared with weekly paclitaxel. However, members considered that ideally PHARMAC staff should conduct a cost utility analysis.
- 5.8 The Committee agreed with BSIG that although there was evidence demonstrating similar efficacy of both paclitaxel and docetaxel in combination with anthracyclines in the adjuvant treatment of early breast cancer there was no evidence supporting use of paclitaxel with anthracycline sparing regimens. Members considered that there was probably a class effect across taxanes, therefore, it was plausible that paclitaxel could be used as effectively as docetaxel in anthracycline sparing regimens, however, members accepted that the absence of clinical trial data meant this was not directly based on comparative trial evidence.
- 5.9 The Committee considered that it would be appropriate to fund docetaxel for the adjuvant treatment of patients with early breast cancer in whom anthracycline treatment is contraindicated. Members considered that older age (>65 years) should not be considered an automatic contraindication for anthracycline treatment, noting that the oldest patient in the Sparano study was 84 and these patients all received doxorubicin.
- 5.10 The Committee considered that the current adjuvant treatment for patients with early breast cancer in whom anthracycline treatment is truly contraindicated, ie those with established or unacceptably high risk of cardiomyopathy, would be CMF chemotherapy (cyclophosphamide, methotrexate and 5FU). Members considered that this was an inferior adjuvant treatment compared with taxane based treatment.

## 6 Lacosamide (Vimpat) for treatment-resistant epilepsy

### Application

- 6.1 The Committee reviewed an application from UCB Australia for the listing of lacosamide (Vimpat) on the Pharmaceutical Schedule as an add-on treatment for patients with partial onset epilepsy who have received inadequate control from at least one first-line anti-epileptic treatment and two second-line adjunctive anti-epileptic treatments.

### Recommendation

- 6.2 The Committee **recommended** that the application for the funding of lacosamide (Vimpat) as an add-on treatment for patients with partial onset epilepsy who have received inadequate control from at least one first-line anti-epileptic treatment and two second-line adjunctive anti-epileptic treatments be declined, on the basis that there are cheaper alternative options that it would be reasonable to try at that point in the treatment paradigm.
- 6.3 The Committee **recommended** that lacosamide (Vimpat) be funded as an add-on treatment for patients with partial onset epilepsy who have received inadequate control

from previous treatments, subject to the following Special Authority criteria, with a medium priority:

Initial application from any relevant practitioner. Approvals valid for 15 months for applications meeting the following criteria:

All of the following:

- 1 Patient has partial onset epilepsy; and
- 2 Seizures are not adequately controlled by, or patient has experienced unacceptable side effects from an optimal treatment with all of the following; sodium valproate, carbamazepine, phenytoin sodium, lamotrigine, topiramate and levetiracetam (see Notes); and
- 3 Patient is currently taking at least two antiepilepsy treatments.

Notes: "Optimal treatment" is defined as treatment which is indicated and clinically appropriate for the patient, given adequate doses for the patient's age, weight and other features affecting the pharmacokinetics of the drug with good evidence of compliance. Women of childbearing age are not required to have a trial of sodium valproate.

Renewal from any relevant practitioner. Approvals valid for 2 years where the patient has demonstrated a significant and sustained improvement in seizure rate or severity and/or quality of life compared with that prior to starting lacosamide treatment (see Note).

Note: As a guideline, clinical trials have referred to a notional 50% reduction in seizure frequency as an indicator of success with anticonvulsant therapy and have assessed quality of life from the patient's perspective.

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;* (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

- 6.4 The Committee noted that lacosamide is a functionalised amino acid (D-serine) anti-epileptic. Its precise mechanism of action is not known but *in vitro* lacosamide selectively enhances slow inactivation of voltage-gated sodium channels resulting in stabilisation of hyperexcitable neuronal membranes. It is indicated as an add-on therapy in the treatment of partial onset seizures with or without secondary generalisation in patients 16 years or older. The Committee noted that the supplier was seeking funding for lacosamide in patients who had tried at least one first-line anti-epileptic agent and at least two second-line adjunctive anti-epileptic agents.
- 6.5 The Committee considered that there was a reasonably large range of funded antiepilepsy treatments and that there were generally few problems with access to these treatments; however, the Committee noted that there would always be a small proportion of patients who continue to have seizures despite having tried all suitable funded options. The Committee noted that the evidence suggests that there may be a higher prevalence of epilepsy among Māori compared with the overall population.

- 6.6 The Committee considered that the evidence provided by the supplier in support of the application was of good quality, consisting of three medium-sized randomised controlled pivotal trials (one phase 2b study and two phase 3 studies), which have been published in peer reviewed journals. In addition, the supplier provided long-term safety data from clinical trial extensions and a meta-analysis of the randomised controlled trials.
- 6.7 All the pivotal trials were randomised, double-blind, multicentre, placebo-controlled, parallel-group trials investigating the efficacy and safety of lacosamide 200 mg, 400 mg and/or 600 mg (depending on the trial) as adjunctive therapy in patients with partial seizures with or without secondary generalisation (Ben-Menachem et al. *Epilepsia* 2007;48(7):1308-17; Chung et al. *Epilepsia* 2010;51(6):958-67; Halasz et al. *Epilepsia* 2009;50(3):443-53). All patients were adults over the age of 16 who had uncontrolled epilepsy despite prior treatment with at least two anti-epileptics. Patients were taking one, two or three concomitant anti-epileptic treatments. In each trial, patients were entered into an eight-week baseline phase and only those who reported  $\geq 4$  partial-onset seizures per 28 days, with seizure-free period no longer than 21 days during the baseline phase, were randomised. After randomisation, patients were titrated up to the randomised dose of lacosamide or placebo over four or six weeks, followed by a 12-week maintenance phase. Patients then transitioned to 200 mg/day prior to entry into an extension study or entered a three-week taper phase. In all trials the primary outcome measures were change in seizure frequency per 28-days and proportion of patients with  $\geq 50\%$  reduction of seizure frequency from baseline to the maintenance phase.
- 6.8 The Committee considered that the results of the trials supported the efficacy of lacosamide 400 mg and 600 mg in reducing seizure frequency in patients with refractory epilepsy compared with placebo for both primary outcome measures, noting that the outcomes for patients on lacosamide 200 mg were not statistically significantly greater than those in the placebo groups. However, the Committee noted that even in the lacosamide 400 mg and 600 mg groups the response rates were not high (approximately 38%–41% of lacosamide 400 mg or 600 mg patients had  $\geq 50\%$  reduction in seizure frequency compared with 18%–26% of placebo patients) and very few patients were seizure free over the 28-day period.
- 6.9 The Committee noted that the supplier had provided a *post-hoc* analysis of the clinical trials to examine the efficacy of lacosamide in patients that would be targeted by the proposed Special Authority criteria. The Committee noted that the results of this analysis suggested that more lacosamide-treated patients in this subgroup achieved a  $\geq 50\%$  reduction in seizure frequency compared to placebo patients in the subgroup, and that the supplier concluded that the responder rate observed in the randomised controlled trials was representative of the response that would be achieved in patients meeting the proposed criteria.
- 6.10 The Committee noted that although the recommended daily dose of lacosamide on the Medsafe datasheet is 400 mg per day, it appeared from the clinical trials that patients on the 600 mg dose may have a better response than those on the 400 mg dose, and given that a reasonable proportion of patients were able to tolerate this dose (600 mg) in the clinical trials it was likely that in clinical practice higher doses would be used. The Committee noted that this was occurring with patients taking levetiracetam through Levetiracetam Special Access, where doses considerably higher than the Medsafe-recommended doses were sometimes being used.

- 6.11 The Committee noted that the main side effects of lacosamide reported in the clinical trials were dizziness and vertigo, unsteady gait, headache, nausea, vomiting and diplopia, and that a relatively high proportion of patients in the clinical trials withdrew because of side effects (19% in the lacosamide 400 mg group and 30% in the 600 mg group, compared with 5% in the placebo group). Other side effects subsequently reported and added to the datasheet included rash, bradycardia, confusional state, suicidal ideation, suicide attempts and syncope. The Committee considered that the results of the extension studies suggest that lacosamide has an acceptable long-term safety profile; however, the Committee considered that it would be important to continue to monitor for emerging side effects given that this was still a relatively new treatment.
- 6.12 The Committee noted that the supplier had not provided a cost-utility analysis (CUA) but had instead provided a cost-effectiveness analysis (CEA). The Committee considered that the supplier should have provided a CUA as this would be required in order to compare the cost-effectiveness of lacosamide with other pharmaceuticals under consideration for funding, noting that this was stated in PHARMAC's funding application guidelines.
- 6.13 The Committee noted that the supplier considered that the appropriate comparator for lacosamide in cost-effectiveness analyses was no treatment, because no other treatment had demonstrated clinical trial efficacy in the patient group for whom lacosamide funding was sought. The Committee considered that the evidence supported the use of lacosamide as a last-line add-on treatment and from that perspective it was reasonable to use placebo as the comparator. However, the Committee noted that there would be multiple other funded treatment options for patients meeting the Special Authority criteria proposed by the supplier, many of which would be reasonable to try at that point in the treatment paradigm. The Committee noted that it would be difficult to compare the efficacy of lacosamide with other possible funded options because there were no comparative trials available. However, the Committee considered that if a CUA was to be performed for lacosamide under the criteria proposed by the supplier, it would be reasonable to use levetiracetam as a comparator as this was the treatment currently being used at that point in the treatment paradigm.
- 6.14 The Committee noted that in a rapid CUA performed by PHARMAC staff, which assumed that lacosamide would be used as a last-line add-on treatment; lacosamide at a dose of 300 mg per day was associated with a cost per quality adjusted life year (QALY) of approximately \$60,000 to \$100,000. The Committee noted that the cost per QALY was likely to be higher if higher doses (eg 400 mg–600 mg per day) were used in the analysis.
- 6.15 The Committee noted the large cost differential between lacosamide and all other funded treatments, including generic levetiracetam (which is due to be funded from 1 November 2010).
- 6.16 For the above reasons, the Committee considered that, at a minimum, patients should be required to have a trial of sodium valproate carbamazepine, phenytoin sodium, lamotrigine, topiramate and levetiracetam, and should be taking at least two current treatments, before accessing funded lacosamide. The Committee noted that sodium valproate has a high risk of teratogenic effects and, therefore, women of childbearing age should not be required to have a trial of sodium valproate prior to accessing lacosamide.

- 6.17 The Committee considered that if it were funded following the treatments outlined in the paragraph above, lacosamide would be used purely as an add-on treatment and would not replace the use of, or delay the use of, any funded treatments.
- 6.18 The Committee considered that the patient numbers estimated by PHARMAC staff was reasonable (being approximately double the patient numbers suggested by the supplier) and that no cost-offsets should be included in the budget impact analysis.
- 6.19 The Committee considered that it would be useful to know whether lacosamide was effective in the subgroup of patients in the clinical trials that had previously received inadequate benefit from levetiracetam, noting that these data should be available because a relatively high proportion of patients in the trials had tried levetiracetam. The Committee considered that this information could help determine whether lacosamide is efficacious following failure of treatment with levetiracetam.

## 7 Naltrexone for Henoch-Schönlein purpura

### Application

- 7.1 The Committee reviewed a preliminary application from a patient requesting the listing of low-dose naltrexone on the Pharmaceutical Schedule for the treatment of Henoch-Schönlein purpura.

### Recommendation

- 7.2 The Committee **recommended** that the application for low-dose naltrexone for the treatment of Henoch-Schönlein purpura be declined on the basis of lack of evidence.

The Decision Criteria particularly relevant to this recommendation are: *(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, (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

- 7.3 The Committee noted that naltrexone is indicated for use within a comprehensive treatment programme for alcohol dependence and as adjunctive therapy in the maintenance of formally opioid-dependent patients who have ceased the use of opioids such as diamorphine (heroin) and morphine.
- 7.4 The Committee noted that naltrexone, used in doses approximately one-tenth those used for the treatment of alcohol addiction, is being prescribed as an "off label" treatment for various autoimmune disorders and some types of cancers.

- 7.5 The Committee noted that, with the exception of two open-label pilot studies in Crohn's disease and irritable bowel syndrome, there does not appear to be any published clinical trial evidence for the use of low-dose naltrexone in any other disorder, including Henoch-Schönlein purpura.

## 8 Paliperidone depot injection (Invega Sustenna) for schizophrenia

### Application

- 8.1 The Committee reviewed an application from Janssen-Cilag for funding of paliperidone depot injection (Invega Sustenna) for the treatment of schizophrenia, subject to the same Special Authority criteria as risperidone depot injection (Risperdal Consta).

### Recommendation

- 8.2 The Committee **recommended** that paliperidone depot injection be listed on the Pharmaceutical Schedule subject to Special Authority criteria similar to those applying to risperidone depot injection only if it was cost-neutral or cost-saving versus risperidone depot injection.

The Decision Criteria particularly relevant to this recommendation are: *(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; (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

- 8.3 The Committee noted that paliperidone (9-hydroxyrisperidone) is the major active metabolite of risperidone.
- 8.4 The Committee noted that the funding application for paliperidone depot injection had been reviewed by the Mental Health Subcommittee in June 2010. The Subcommittee recommended that paliperidone depot injection be listed on the Pharmaceutical Schedule subject to Special Authority criteria similar to risperidone depot injection, and that this recommendation should be considered a low priority within the context of the mental health therapeutic area.
- 8.5 The Committee noted that the key study provided in support of the application, PSY-3006, had not been published in a peer reviewed journal; the Committee noted its general view that funding applications should be supported by published clinical trial evidence reported in a reputable peer-reviewed journal. However, the Committee considered that the evidence provided suggested that paliperidone depot injection is associated with similar efficacy to risperidone depot injection.

- 8.6 The Committee agreed with the views of the Mental Health Subcommittee relating to the application, noting that although there were some advantages of paliperidone depot injection such as it not requiring refrigeration and being relatively fast-acting, the monthly injection schedule was unlikely to significantly alter patients' contact with healthcare workers and it was likely that patients would still require cover with oral antipsychotics when starting treatment.
- 8.7 In addition, the Committee noted that the studies provided by the supplier were of short duration, which did not reflect clinical practice given that paliperidone depot injection is intended to be a longer-term maintenance treatment. The Committee considered that the duration of the studies was not long enough to accurately assess the emergence of longer-term side effects such as extrapyramidal side effects, noting that it was theoretically possible that paliperidone could be associated with a higher incidence of side effects than risperidone.
- 8.8 Overall, the Committee considered that paliperidone depot injection offered only a small practical clinical benefit over risperidone depot injection.

## 9 Riluzole (Rilutek) for amyotrophic lateral sclerosis

### Application

- 9.1 The Committee reviewed additional information provided by Sanofi-Aventis New Zealand Limited in support of its application for the listing of riluzole (Rilutek) on the Pharmaceutical Schedule for the treatment of amyotrophic lateral sclerosis.

### Recommendation

- 9.2 The Committee reiterated its previous **recommendation** that the application for riluzole (Rilutek) for the treatment of amyotrophic lateral sclerosis be declined.

The Decision Criteria particularly relevant to this recommendation are: (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

- 9.3 The Committee noted that it had reviewed an application from Sanofi-Aventis for the listing of riluzole (Rilutek) for amyotrophic lateral sclerosis (ALS) at its meeting in August 2009 and had recommended that the application be declined, because of its poor efficacy, high cost and poor cost effectiveness.
- 9.4 The Committee noted that the supplier had subsequently provided additional information and comment for PTAC's review, including updated (lower) pricing.

- 9.5 The Committee noted that the supplier considered that the Cochrane review of riluzole (Miller et al. Cochrane Database of Systematic Reviews 2007, Issue 1) was flawed because it did not take risk factors into account when assessing the trials and it included a trial in older patients with more advanced disease (which did not show a benefit from riluzole) which effectively offset the benefit found in two earlier trials included in the analysis.
- 9.6 The Committee noted that the three randomised clinical trials included in the Cochrane review are the only available randomised trials (with the exception of a Japanese trial for which results have not been published in the English language) and, as such, it was appropriate to take results of all the trials into consideration.
- 9.7 The Committee considered that it could be possible to interpret the randomised trials as showing a greater benefit of riluzole in younger patients with milder disease; however, the Committee considered that this was not definitively shown and the evidence was not strong enough to support applying targeting criteria in an attempt to prospectively identify patients more likely to benefit.
- 9.8 The Committee noted that the supplier had provided a number of non-randomised, open label cohort studies in support of its claim that 'real world' use of riluzole demonstrates benefit greater than that reported in the Cochrane review (where riluzole was estimated to improve survival by 2.3 months). The studies were Murphy et al. Neurology 2008;71:1889-95; Lacomblez et al. Amyotroph Lateral Scler Other Motor Neuron Disord 2002;3(1):23-9; Zoccolella et al. Eur J Neurol 2007;14:262-8; Traynor et al. J Neurol 2003;250:473-9 and Mitchell et al. Amyotroph Lateral Scler 2006;7(2):67-71. The Committee considered that the quality of this evidence was relatively weak and was not sufficient to support changing the overall estimated benefit of riluzole in any analyses.
- 9.9 The Committee noted that the supplier had provided an economic analysis in its current submission, which included scenarios additional to those included in PHARMAC's previous rapid analysis. The Committee noted that PHARMAC staff had also updated its rapid analysis, with a resulting cost per quality adjusted life year (QALY) of approximately \$60,000 to \$80,000. The Committee considered that the assumptions used in the PHARMAC staff analysis were reasonable. The Committee considered that the extrapolation of overall survival gains over an 80-month timeframe in the supplier's analysis was speculative, because it was based on non-randomised cross-over trials where poor responders had dropped out. The Committee noted that tracheostomy was a less likely option for patients in the later stages of the disease because of a change in the standard of care for airway support. In the New Zealand setting patients would more likely receive non-invasive ventilation with CPAP (constant positive airway pressure) or BiPAP (bilevel positive airway pressure).
- 9.10 The Committee noted that even with the proposed price reduction, riluzole was still a very expensive treatment with little evidence of significant clinical benefit.

## **10 Deferasirox (Exjade) and deferiprone (Ferriprox) for iron overload**

## Application

- 10.1 The Committee reviewed a re-submission from Novartis for deferasirox (Exjade) with additional information regarding its efficacy compared to deferiprone (Ferriprox) for the treatment of transfusional iron overload secondary to congenital inherited anaemias and its efficacy in the treatment of transfusional iron overload secondary to acquired anaemias. Additional information from Orphan Australia to support deferiprone's efficacy in the treatment of transfusional iron overload secondary to congenital inherited and acquired anaemias was also reviewed.

## Recommendation

- 10.2 The Committee considered that deferiprone (Ferriprox) was efficacious as monotherapy for the treatment of transfusional iron overload secondary to congenital inherited anaemia. Combination therapy with deferiprone and desferrioxamine is superior to either treatment alone. The Committee reiterated their previous **recommendation** that deferiprone (Ferriprox) should be listed with high priority for the treatment of transfusional iron overload secondary to congenital inherited anaemia.
- 10.3 The Committee **recommended** that deferasirox (Exjade) be funded with high priority as second-line treatment for certain patient groups with transfusional iron overload secondary to congenital inherited anaemia namely children under six years of age and patients for whom deferiprone is contraindicated. The Committee **recommended** that the Cancer Treatments Subcommittee of PTAC (CaTSoP) review this application to define the Special Authority criteria.
- 10.4 The Committee considered that the clinical evidence to support the use of oral iron chelators in the treatment of transfusional iron overload secondary to acquired anaemias is currently insufficient. The Committee **recommended** that the decision to fund oral iron chelators for the treatment of transfusional iron overload secondary to acquired anaemias be deferred until it is reviewed by CaTSoP.

The Decision Criteria particularly relevant to this recommendation are: (i) *The health needs of all eligible people within New Zealand;* (iii) *The availability and suitability of existing medicines, therapeutic medical devices and related products and related things;* (iv) *The clinical benefits and risks of pharmaceuticals;* (vi) *The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

## Discussion

- 10.5 The Committee noted that PHARMAC has reached a provisional agreement with the supplier of deferiprone (Ferriprox) to list it subject to PHARMAC Board approval, restricted by Special Authority to patients with chronic transfusional iron overload secondary to congenital inherited anaemia. The Committee agreed that although the restriction is wider than previously recommended, it is appropriate as it is difficult to define patient intolerance to desferrioxamine given it is an injection which is less tolerated than an oral treatment. The Committee also noted that the proposed restriction would allow deferiprone to be used in combination with desferrioxamine for patients with significant cardiac iron overload or patients chelating inadequately with desferrioxamine which was in-line with their previous recommendation.

- 10.6 The Committee reviewed additional information from Novartis in regards to deferasirox, suggesting its superior efficacy compared to deferiprone for the treatment of transfusional iron overload secondary to congenital inherited anaemias.
- 10.7 The Committee reviewed the EPIC study which was a large prospective, multicentre, open label, observational study involving 1744 patients with transfusion related siderosis due to thalassaemia, MDS, aplastic anaemia, sickle cell disease and other transfusional anaemias. Of the 79.6% of patients who completed the study, 51% received 30mg/kg/day or more. Overall there was a statistically significant reduction of median ferritin. In the thalassaemia patients, statistically significant reduction was seen only at doses above 30mg/kg/day. 10% of patients had more than 33% increase in creatinine and 1 patient had drug related acute renal failure. The Committee considered the EPIC study, although not controlled with placebo or a comparator arm suggests that deferasirox is effective in reducing serum ferritin but it highlighted the need to use higher doses to maintain this benefit especially in patients with thalassaemia.
- 10.8 The Committee noted that Pennell et al (Blood 2010;115(12):2364) studied 192 patients with beta-thalassaemia in a cardiac sub study of the EPIC. Patients were divided into 2 treatment arms; cardiac iron reduction arm (T2\* 5-20 ms) and cardiac iron prevention arm (T2\* >20ms). At 12 months, 63.2% and 47.4% of patients in the reduction and prevention arms respectively were receiving 40mg/kg/day of deferasirox. The T2\* in the reduction arm was significantly improved. However, 16.2% of patients in this arm showed worsening of T2\* suggesting some patients may not respond. In the prevention arm, T2\* remained stable and the ejection fraction increased by 2%.
- 10.9 The Committee also considered the ESCALATOR study and it noted that the journal publication was not included in the application. It was an open label observational study involving 239 patients. The primary efficacy endpoint was reduction in liver iron concentration (LIC) and treatment success was achieved in 57% of patients which was statistically significant. Members noted that follow-up results from this trial, which was presented in abstract form, indicate that benefits were maintained over time. A cardiac sub study from the ESCALATOR trial involved 19 patients and mean doses of deferasirox increased to 37.7mg/kg/day at 18 months. The cardiac T2\* was significantly improved at 6 and 18 months.
- 10.10 The Committee noted that results from a four-year extension of the pivotal DFX trial in abstract form (Capellini et al 2009) showed ongoing benefits of deferasirox and reasonable tolerability long term.
- 10.11 The Committee considered evidence relating to the efficacy of deferasirox in reducing labile plasma iron (LPI) and non-transferrin bound iron (NTBI). Zanninelli et al (BJH 2009;147:744) monitored LPI over 24 hours in 40 thalassaemia patients on chelation therapy. Analysis showed that deferasirox achieved sustained reductions in LPI in more patients than treatment with desferrioxamine alone or deferiprone alone.
- 10.12 Based on the studies reviewed, the Committee considered that deferasirox was efficacious in reducing serum ferritin and LIC but the trials indicate that higher doses were needed to reduce cardiac iron. Neither the EPIC nor the ESCALATOR study provided grade 1 evidence. The Committee noted that NTBI and LPI are surrogate markers that may have an important role in determining the need for chelation. The Committee considered that even though this hypothesis is attractive in explaining

increased oxidative stress, the prognostic significance of LPI and NTBI need to be proven by proper clinical trials with hard endpoints. The Committee considered that deferasirox is an effective oral iron chelator but there are a proportion of patients who may not respond. The Committee noted that deferasirox has safety issues but they are well-established.

- 10.13 The Committee reviewed new clinical evidence for deferiprone supporting its use as monotherapy in congenital inherited anaemias. An observational study by Ceci et al (*Haematologica* 2006;91:1420) showed that good compliance with chelation therapy and the use of deferiprone were independent predictors of survival. Modell et al (*JCMR* 2008;10:42) examined 850 patients from the British Thalassaemic Registry and revealed that life expectancy has markedly increased over the years (1970-2000). The Committee noted that the success was attributed to bone marrow transplantation in younger patients, development of T2\*, introduction of deferiprone and combination treatment with desferrioxamine. The Committee noted that Maggio et al (*Blood Cells Mol Dis* 2009;42:247) conducted a prospective survival study of patients from a previous trial; this showed that 11 deaths occurred in the desferrioxamine group, 1 death occurred in the sequential desferrioxamine-deferiprone group and no deaths in the deferiprone or combination desferrioxamine and deferiprone group over a follow up period of 5 years.
- 10.14 The Committee noted that Pennell et al (*Blood* 2006;107(9):3738) randomised 61 patients to treatment with desferrioxamine or deferiprone for 1 year. Improvements of T2\* and ejection fraction were significantly better in the deferiprone compared to the desferrioxamine group. Liver iron concentration and ferritin levels between the 2 treatments were not different. Farmaki et al (*BJH* 2009;148:466) showed that in 52 patients who were intensively chelated with combination deferiprone and desferrioxamine, at 5 years none had increased liver iron and only 2 had increased cardiac iron. 15 of the 18 patients who had cardiac dysfunction at baseline improved. The Committee noted that neutropenia was the main side-effect.
- 10.15 The Committee considered that deferiprone is an effective iron chelator when used alone or in combination with desferrioxamine and it is especially effective in reducing cardiac iron. The Committee considered that combination therapy is superior to either treatment alone. As previously discussed, deferiprone may not be very effective in chelating liver iron. However, deferiprone has been shown to have survival benefits and its safety profile is well understood.
- 10.16 The Committee considered deferiprone and deferasirox have similar therapeutic effects but have not been directly compared in a randomised controlled trial. Advantages of deferasirox are that it is taken once daily. Although deferasirox does not require weekly blood monitoring like deferiprone, its Medsafe datasheet does recommend that monthly blood monitoring be performed. The Committee considered that there is no clinical reason not to list deferasirox as first line therapy for transfusional iron overload in congenital inherited anaemias but it could be limited by Special Authority to certain patient groups due to its high cost relative to deferiprone. The Committee considered that it would be appropriate to limit deferasirox to children under six years of age and to patients contraindicated to deferiprone. The Committee considered that deferiprone has better long term outcome data and cardiac iron reduction data as compared to deferasirox. It requires administration three times daily and closer monitoring due to the risk of agranulocytosis but these patients are closely monitored now anyway. The agranulocytosis caused by deferiprone is also reversible.

- 10.17 The Committee considered clinical evidence from both suppliers regarding the efficacy of deferiprone/deferiasirox in transfusional iron overload secondary to acquired anaemias. The Committee considered that there was some evidence that deferiasirox is effective for iron chelation in myelodysplasia (MDS), aplastic anaemia and pure red cell aplasia. In the EPIC study, all these groups showed statistically significant reduction in serum ferritin. In these groups, the mean dose of deferiasirox was below 20mg/kg/day. Other small studies also suggested that deferiasirox could reduce ferritin levels and LPI levels in MDS. The Committee noted that there were no prospective studies on iron chelation therapy in patients with paroxysmal nocturnal haemoglobinuria (PNH) or stem cell transplants. The Committee considered that there was limited evidence in the form of case series to support the use of deferiprone in the treatment of acquired anaemias.
- 10.18 The Committee reviewed several observational studies concerning the use of deferiasirox in MDS (Rose et al 2010, Raptis et al 2009, Fox et al 2009, Takatoku et al 2007 and Malcovati et al 2005). These studies showed a survival advantage in patients treated with deferiasirox. The entry criteria for chelation were different in the different studies. The Committee considered an increase in mortality in transfused patients could be due to severity of the disease among transfused patients compared to those who did not receive transfusions. The Committee considered that In most studies, patients who had chelation therapy were four to five years younger than the general MDS population, and physicians may have offered chelation therapy to patients who were relatively well. The Committee considered that even with the adjustments done to reduce bias, these adjustments are unlikely to eliminate bias completely. The Committee considered that only well designed randomised controlled trials could establish the real benefit of iron chelation therapy in patients with MDS.
- 10.19 The Committee noted that deaths due to iron overload occur in the second decade of life in patients with untreated congenital inherited anaemias. The Committee considered that most patients with MDS may not develop significant cardiac iron overload. The Committee noted two publications looking at cardiac iron overload in MDS. Konen and others (AJH 2007;83:611-13) conducted a cardiac and liver MRI study to determine the iron content of 10 patients with MDS, and on average, each patient was transfused with 90 units of blood. The Committee noted that none of the patients had raised cardiac iron but had raised liver iron. A similar study by Chacko (BJH 2007;138:587-593) showed results of low or absent myocardial iron but the presence of significant liver iron in 11 heavily transfused MDS patients. The Committee noted that the study patients had normal left ventricular function.
- 10.20 The Committee noted the study by Chee and others from the Mayo clinic AJH 2008;83(8):611-613. The Committee considered that this retrospective observational study of 126 adult patients with low risk MDS (RARS or refractory anaemia with ringed sideroblasts), showed that the IPSS score and need for red blood cell (RBC) transfusion at the time of diagnosis were highly predictive of mortality. The Committee further considered that the number of RBC units transfused, serum ferritin at the time of diagnosis, or follow up were not associated with increased mortality, and there was no association between mortality and stratified ferritin levels. The Committee noted that the causes of death were not clearly described in all individuals but the deaths due to iron overload appear to be very rare in this group. The Committee also considered that this study could also have significant bias.

10.21 Following review of these studies, the Committee considered that there was no hard outcome data to recommend oral iron chelation therapy for patients with MDS or other acquired anaemias at this time. However, the Committee considered that there may be a small number of young patients with acquired anaemias with significant iron overload (including cardiac iron overload) who could potentially benefit from iron chelation therapies. This group may need to be identified with techniques such as T2\* cardiac MRI, and such groups may potentially benefit from iron chelation therapies. The Committee considered that funding oral iron chelators for patients with MDS and raised ferritin could pose a significant fiscal risk given the relatively large patient numbers. The Committee considered seeking further advice from CaTSoP in regards to the benefits of iron chelation therapies in acquired anaemias and other indications such as stem cell transplants.

## 11 Prasugrel for acute coronary syndromes

### Application

11.1 The Committee reviewed a re-submission from Eli Lilly for prasugrel after PTAC previously recommended its application for funding be declined.

### Recommendation

11.2 The Committee **recommended** that the decision to fund prasugrel be deferred until it is reviewed by the Cardiovascular Subcommittee of PTAC.

### Discussion

11.3 The Committee noted that Eli Lilly chose to define the appropriate patient groups for prasugrel reimbursement based on the recommendations by the National Institute for Health and Clinical Excellence (NICE). The first group that was suggested was for patients with ST segment myocardial infarctions (STEMI). Members noted the supplier's comment that these patients usually progress to the catheter laboratory immediately hence may not have time to achieve optimal inhibition of platelet aggregation prior to percutaneous coronary intervention (PCI) if treated with clopidogrel. However, the Committee considered that when this specific subgroup was considered, there was no benefit observed (Montalescot et al, Lancet 2009:373:723) with a hazard ratio (HR) for primary PCI for STEMI being 0.8 (0.60-1.08). The Committee noted that this data was not available to NICE at the time of assessment. The Committee also noted that two thirds of the STEMI PCIs within TRITON were primary PCIs, and it was only in the remaining one third of STEMIs which were treated with delayed PCIs that a statistically significant improvement was seen. However, the Committee considered that this group also had a delayed clopidogrel administration, which would not be considered to be current standard of care. The Committee considered that there was limited clinical evidence to support funding prasugrel for patients undergoing primary PCI post STEMI.

11.4 The Committee noted that the supplier also highlighted that patients with stent thrombosis could benefit from treatment with prasugrel. However, the Committee

considered that the TRITON study did not provide evidence for the role of prasugrel post stent thrombosis so there are only theoretical reasons to currently support this indication.

- 11.5 The Committee noted that the supplier provided some responses to the issues PTAC raised when they reviewed the application in February 2010. The Committee noted that the supplier disagreed with PTAC's previous comment that overall prasugrel offered a modest benefit with an increased risk of haemorrhage. On review of the data from the initial and subsequent TRITON publications, the Committee noted that it does not dispute that a statistically significant benefit has occurred but it does question whether this benefit is real or as a result of the way the comparator has been used. The Committee considered that there were significant methodological issues with both the timing and dosage of clopidogrel, and that for the group where the delay in clopidogrel was minimised (i.e. those undergoing primary PCI for STEMI), there was no benefit of prasugrel over clopidogrel.
- 11.6 The Committee considered that the issue of possible inadequate initial dosing of clopidogrel within the TRITON study has now been confirmed with the unpublished CURRENT OASIS 7 which used higher dosages of clopidogrel (600mg loading then 150mg daily for the first seven days). A higher clopidogrel loading dose is reflective of current New Zealand practice. The Committee considered that in the subgroup most comparable to the TRITON study population (i.e. those undergoing PCI), there was significant benefit in both composite endpoints (day 30 HR 0.85 (0.74-0.99),  $p=0.036$ ) and in stent thrombosis rates (HR 0.71(0.57-0.89),  $p=0.02$ ) with the usage of the higher clopidogrel dosages. The Committee noted that clopidogrel was also commenced at presentation rather than on the catheter table as occurred for the majority of TRITON study patients which was closer to standard clinical practice. Although the Committee agreed that the benefit of prasugrel continued beyond the loading period, the Committee considered that any statistical benefit seen in the TRITON study may be a reflection of the initial delayed and inadequate clopidogrel dosing of clopidogrel.
- 11.7 The Committee considered that Wiviott et al (Circulation 2008;118:1626) showed a net benefit only for the diabetic population which made up 23% of the study cohort ( $p=0.001$ ) compared to no net benefit for the non-diabetic population ( $p=0.16$ ). As a result, the non-diabetic population had a number needed to treat (NNT) of  $>100$  despite concerns on the methodology. The results from the CURRENT OASIS 7 study could show further evidence regarding the impact of clopidogrel when used earlier and at a higher loading dose in the diabetic population. Based on all the reasons discussed, the Committee considered that their previous statement that prasugrel only offered a modest benefit was appropriate.
- 11.8 The Committee considered that prasugrel is associated with an increased risk of haemorrhage. Wiviott et al (NEJM 2007;357:2001) states that major bleeding, life-threatening bleeding and fatal bleeding were all statistically significantly increased, and the risk of haemorrhage was found to be equivalent only when subgroups were examined.
- 11.9 In response to the supplier's rebuttal that prasugrel significantly reduced the risk of spontaneous and procedural MIs and that spontaneous MIs have been demonstrated to be a powerful predictor of mortality, the Committee considered that the majority of MIs seen in the TRITON study were procedure related (Morrow et al. Circulation 2009;119:2758). The Committee also considered that Prasad et al (J Am Coll Cardiol

2009;54:477) has shown that periprocedural MI was not a significant predictor of mortality.

- 11.10 The Committee considered that it is important to take into account the fact that prasugrel is significantly more expensive than clopidogrel, considering it only offers modest benefits. The Committee also considered that a shorter duration of prasugrel would make it more cost-effective, but there is inadequate evidence that the benefits are substantial. The Committee also noted that the FDA has not allowed a superiority claim for prasugrel over clopidogrel and have highlighted potential cancer signals growing over time after prasugrel use.
- 11.11 The Committee noted that data on Māori rates of CYP2C19 polymorphisms have been quoted at 24% (Lea et al. NZMJ 2008;121:33). However, the Committee noted that the authors state that “due to the fact that the Māori sample studied here was selected to possess as little non-Māori ancestry as possible, our allele frequencies should not be interpreted to be estimates of the general Māori population”. Therefore, the rate is likely to be less than 24%. The Committee also noted that the 45% of Pacific Peoples studied related to Papua New Guinea and Vanuatu rather than Polynesian populations, and data on Polynesian populations is unknown. Mega et al (NEJM 2009;360:354) also showed that increasing the loading and maintenance dosage of clopidogrel increases the exposure to the active metabolite of clopidogrel and reduces maximal platelet aggregation even in those with CYP2C19 polymorphism. The Committee considered that the genetic analysis of CURRENT OASIS 7 would help shed light on this issue.
- 11.12 The Committee noted that PHARMAC had received four applications for prasugrel through HEC for patients who were allergic to clopidogrel. The Committee also noted that prior to prasugrel being available approximately 21 HEC/CEC applications for ticlopidine in clopidogrel-allergic patients were approved. The Committee noted that ticlopidine was associated with a 2.3% rate of neutropenia. However, due to the lack of evidence to support the use of prasugrel currently, the Committee considered that it was appropriate for ticlopidine to be recommended for clopidogrel-allergic PCI patients.

## 12 Sitagliptin with metformin (Januvia/Janumet) for diabetes

### Application

- 12.1 The Committee reviewed a re-application from Merck Sharpe and Dohme for the listing of sitagliptin (Januvia) and the listing of its combination sitagliptin and metformin formulation (Janumet) on the Pharmaceutical Schedule for the treatment of patients with type 2 diabetes.

### Recommendation

- 12.2 The Committee **recommended** that the application for sitagliptin (Januvia) and sitagliptin and metformin (Janumet) for the treatment of patients with type 2 diabetes be declined.
- 12.3 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.*

## **Discussion**

- 12.4 The Committee noted sitagliptin was first reviewed for funding in May 2008 and further reviewed in November 2009 along with the combination sitagliptin and metformin funding application. The Committee noted that these applications had been declined. The Committee noted that the Diabetes Subcommittee of PTAC had recommended sitagliptin be listed with a low priority, and that combination sitagliptin and metformin be listed only if cost-neutral or cost-saving compared with sitagliptin and metformin alone.
- 12.5 The Committee noted that the supplier, in response to the previous review by PTAC, had provided a review of the cumulative safety data for sitagliptin and sitagliptin/metformin (particular focus around the incidence of pancreatitis), published data relating to the safety and efficacy of sitagliptin over 2 years, information relating to updated international guidelines on type 2 diabetes and recommendations on the use of newer agents, and further evidence of an unmet clinical need in New Zealand for patients with diabetes.
- 12.6 The Committee noted the published study (Williams-Herman et al. Diabetes Obesity Metab 2010;12:442-451) on the efficacy and safety of sitagliptin and metformin as initial combination therapy and as monotherapy over two years in type 2 diabetes. The Committee noted that this data had previously been seen by PTAC in abstract form.
- 12.7 The Committee noted a review of preclinical and clinical trial data regarding the incidence of pancreatitis with sitagliptin (Engel et al. Int J Clin Pract 2010;64:984-990). The Committee considered that at this stage the causal relationship between sitagliptin and pancreatitis remains unproven, and only continued post marketing adverse event reporting and pharmacoepidemiological examination of large databases will help prove or disprove the association.
- 12.8 The Committee noted that the relevant sections provided by the supplier of the UK National Institute for Health and Excellence clinical guidelines which places DPP-4 inhibitors on the same step as glitazones and behind metformin and sulphonylureas in the stepwise treatment of type 2 diabetes. The Committee noted that it had previously been supplied these guidelines by PHARMAC.
- 12.9 The Committee noted that there was no change in the proposed price and therefore funding sitagliptin would result in a high budget impact and have a high cost per quality-adjusted life year (QALY). Members considered that the supplier needed to reconsider its proposed pricing and take into account the price of other oral hypoglycaemic agents and net-effective insulin preparation prices.
- 12.10 Members considered that there was little new data to support a change in its previous recommendation.

## 13 Bisoprolol for congestive heart disease

### Application

- 13.1 The Committee reviewed a submission from PHARMAC staff for bisoprolol for the treatment of chronic heart failure as an alternative to metoprolol succinate or carvedilol.

### Recommendation

- 13.2 The Committee **recommended** that bisoprolol be listed on the Pharmaceutical Schedule with medium priority for the treatment of chronic heart failure.

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; (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

- 13.3 The Committee noted that PHARMAC intends to run a sole supply process for metoprolol succinate and there is a risk that if one supplier is awarded sole supply, some patients may experience intolerance to it. The Committee noted that both itself and the Cardiovascular Subcommittee have previously considered that carvedilol would be a suitable alternative to metoprolol succinate for the treatment of chronic heart failure. The Committee also noted that some clinicians highlighted that metoprolol succinate would still be preferred over carvedilol for the treatment of chronic heart failure as the latter required twice daily dosing and some patients for example; chronic obstructive pulmonary disease (COPD) and asthma patients could not tolerate a non-selective beta-blocker like carvedilol.
- 13.4 The Committee reviewed clinical evidence from the CIBIS and CIBIS II trials where bisoprolol was compared to placebo for the treatment of chronic heart failure. The Committee noted that there were no direct trials comparing metoprolol succinate to bisoprolol in this indication. The designs of the two trials were similar but CIBIS II involved more patients, 2647 patients versus 641 patients. The Committee noted that the patients in the CIBIS II trial were followed up for a mean of 1.3 years and the trial was stopped prematurely after the results of an interim analysis showed unequivocal benefit for bisoprolol. All-cause mortality was significantly lower with bisoprolol than on placebo; 11.8% *versus* 17.3% deaths ( $p < 0.0001$ ). Significantly fewer patients were admitted to hospital overall for cardiovascular reasons with the active drug however there were a significant excess of hospitalisations for stroke with bisoprolol (2.3% *versus* 1.2%,  $p = 0.04$ ).
- 13.5 The Committee considered that in a meta-analysis of the CIBIS and CIBIS II trials (Leizorovicz et al 2002), bisoprolol was shown to reduce the relative risk of death by 29.3% (12.7% *versus* 17.9%) and it also reduced the relative risk of cardiovascular death, sudden death and hospital admissions compared to placebo. The Committee considered that the clinical trial results for bisoprolol were very similar to those of metoprolol and/or carvedilol.

- 13.6 The Committee considered that the strength and quality of the evidence reviewed for bisoprolol were good. The Committee considered that bisoprolol would be a suitable alternative to metoprolol succinate for the treatment of chronic heart failure as it is a  $\beta_1$  selective beta-blocker. It could also be used for the treatment of hypertension, angina and supraventricular tachycardia (SVT).
- 13.7 The Committee considered that the uptake on bisoprolol would be slow initially as doctors in New Zealand have little or no experience with it, and the listing of bisoprolol is unlikely to be a fiscal risk but this is also dependant on the price. The Committee considered that there was no clinical reason not to open list bisoprolol if an acceptable price could be negotiated. The Committee also considered that bisoprolol would challenge the existing markets for metoprolol and atenolol if listed.

## 14 Azithromycin for post lung transplant bronchiolitis obliterans prophylaxis

### Application

- 14.1 The Committee considered an application from [ withheld under s9(2)(a) of the OIA ] for the prophylactic use of azithromycin in lung transplant recipients for the prevention of bronchiolitis obliterans syndrome (BOS).

### Recommendation

- 14.2 The Committee **recommended** that azithromycin be listed on the Pharmaceutical Schedule for prophylaxis of bronchiolitis obliterans syndrome subject to the following Special Authority criteria, with a high priority:

Initial application from a lung transplant specialist. Approvals valid for 12 months for applications meeting the following criteria:

Prophylaxis of bronchiolitis obliterans syndrome following lung transplantation

Renewal from lung transplant specialist. Application valid without further renewal, unless notified, where the patient remains well and free from bronchiolitis obliterans syndrome.

Note: Prophylaxis of BOS is an unapproved indication (refer to section A: General Rules, Part I (Interpretations and Definitions) and part IV (Miscellaneous Provisions) rule 4.6) off label.

- 14.3 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;* (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**

- 14.4 The Committee noted that the five year survival for lung transplant patients is ~50% and that most of the deaths are due to chronic rejection. Rejection results in inflammation in the lungs resulting in blocking of the bronchioles with granulation tissue. The Committee further noted that this is characterised by a progressive and irreversible decline in FEV1 which is clinically defined as bronchiolitis obliterans syndrome (BOS).
- 14.5 The Committee noted that azithromycin is approved for off-label use via Hospital Exceptional Circumstances (HEC) to treat patients with established BOS and noted that the Respiratory Sub-Committee have recommended funding for this indication. The Committee noted that it is assumed that the beneficial effect is a result of azithromycin's 'anti-inflammatory' and 'immunomodulatory' properties rather than antibiotic action.
- 14.6 The Committee noted that the evidence for the use of azithromycin as a treatment for BOS is not strong with only three published papers all of which were observations or open label studies with small patient numbers. Of those treated with azithromycin, less than 50% of patients see an improvement in FEV1 although results suggest that others stopped deteriorating.
- 14.7 The Committee considered evidence for the use of azithromycin in the prophylaxis of BOS from the Vos et al (ERJ Express 2010) paper that accompanied the application from [ withheld under s9(2)(a) of the OIA ]. The Vos et al trial was a randomised, double blind, placebo controlled trial with 83 patients treated thrice weekly with either azithromycin or placebo initiated at discharge and continued over a period of two years. The Committee considered that while there was no survival gain between the two groups of patients (although this could be explained by the fact that if patients developed BOS, the study drug was stopped and they were given azithromycin open label), various clinical indicators did improve on the azithromycin arm compared to placebo including FEV1, lower airway neutrophilia, lymphocytic bronchiolitis and plasma C-reactive protein levels (CRP). 42% in the placebo arm and 70% in the azithromycin arm completed the study with 44.2% in the placebo arm and 12.5% in the azithromycin arm developing BOS. The Committee noted that two patients discontinued azithromycin due to gastrointestinal adverse events.
- 14.8 The Committee noted that while the use of azithromycin in the treatment of BOS is available via access through HEC, there is currently no access available for prophylaxis. The Committee noted that if the onset of BOS were delayed or less prevalent due to prophylactic treatment with azithromycin then there may be a reduction in the number of admissions, re-transplants and other immunosuppressants leading to savings although at this stage there is no evidence for this.
- 14.9 The Committee noted that they are unlikely to get any better information as there are unlikely to be any bigger trials conducted due to low lung transplant patient numbers internationally.

## 15 Subcommittee minutes

### 15.1 Respiratory Subcommittee Minutes – 5 February 2010

15.1.1 The record of the meeting was noted and accepted.

### 15.2 Anti-Infective Subcommittee Minutes – 8 April 2010

15.2.1 The record of the meeting was noted and accepted.

### 15.3 Cancer Treatments Subcommittee Minutes – 9 April 2010

15.3.1 The Committee reiterated its previous **recommendation** that bevacizumab be listed in the Pharmaceutical Schedule as first-line, neoadjuvant (Pre-surgical), treatment in patients with metastatic colorectal cancer where metastases are confined to the liver only and complete resection is planned. Members considered that bevacizumab should be funded for a maximum of 4 treatment cycles. The Committee gave this recommendation a low priority.

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

### 15.4 Analgesic Subcommittee Minutes – 29 April 2010

15.4.1 The record of the meeting was noted and accepted.

### 15.5 Pulmonary Arterial Hypertension Subcommittee Minutes– 13 May 2010

15.5.1 The record of the meeting was noted and accepted.

### 15.6 Mental Health Subcommittee Minutes – 21 June 2010

15.6.1 The Committee noted that it had not yet reviewed the application for rivastigmine patches (Exelon) and, therefore, did not accept the Subcommittee's recommendation for rivastigmine patches. The Committee **recommended** that it review the rivastigmine transdermal patches application at its next meeting in November 2010.

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

15.7 Ophthalmology Subcommittee Minutes – 14 May 2010

15.7.1 The record of the meeting was noted and accepted.

**16 Minutes of PTAC email meeting held 26 August to 6 September 2010**

16.1 PTAC reviewed the multiple sclerosis minutes of the PTAC meeting held on 25 & 26 February 2010 and revised its view of the utility value for EDSS0-3 in paragraph 17.58 (and the consequent ratio for the rate of utility lost for lower vs. higher EDSS scores (i.e. earlier vs. later)). The Committee made the following amendment:

16.1.1 Paragraph 17.58: replace: “The Committee considered that the data from Naci et al 2010 supported a loss in utility for EDSS0-3 of 0.083 per unit and a loss in utility for EDSS 3-6 of 0.04 per unit, with a resulting 2:1 ratio for the rate of utility lost for lower vs. higher EDSS scores (i.e. earlier vs. later).”

with

16.1.2 “The Committee considered that the data from Naci et al 2010 (using the weighted mean utilities calculated in paragraph 17.36 above) supported average losses in utility of ~~[0.83]~~ **0.10** per unit for EDSS0-3 and 0.04 per unit for EDSS3-6, with a resulting ~~[2:1]~~ **2.5:1** ratio for the rate of utility lost for lower vs. higher EDSS scores (i.e. earlier vs. later).”