Anti-Infective Subcommittee of PTAC
Meeting held 26 February 2014

(minutes for web publishing)

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

The Anti-Infective Subcommittee may:

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

These Subcommittee minutes were reviewed by PTAC at its meeting 8 & 9 May 2014, the record of which will be available in July 2014.

Minutes of the Anti-Infective Subcommittee of PTAC

Meeting held 26 February 2014

1 Therapeutic Group review

1.1 The Subcommittee noted the number of Special Authority approvals for ivermectin since its listing date in 2012. Members noted that the number of ivermectin approvals for use in institutions did not reflect the number of patients being treated under this indication, as only one Special Authority was required for all patients in an institution. The Subcommittee considered that usage was low, and that this low usage was likely due to low awareness of ivermectin's funded availability.

1.2 The Subcommittee noted the request from PTAC regarding the microbiological/ecological impact of widening access to ciprofloxacin eye drops for use in the ear. The Subcommittee considered that there was probably little dissemination of resistant microbes from the ear canal. Members noted that quinolones may have a similar impact on hearing to aminoglycosides. The Subcommittee considered that Sofradex should be considered the first-line agent, and that ciprofloxacin eye drops (for use in the ear) should be second-line and on the recommendation of an ear nose and throat specialist. Members noted that ciprofloxacin eye drops were not registered for use in the ear so this would be prescribed under Section 25 of the Medicines Act – 'off-label prescribing'.

1.3 The Subcommittee considered an application from GlaxoSmithKline for consideration of open listing of cefuroxime axetil at a price that was cost neutral to cefaclor. Members noted that there was no oral liquid presentation of cefuroxime axetil. Members considered that there would be a benefit to patients in having cefuroxime axetil fully funded, as it had a less frequent dosing regimen and better penetration for certain indications such as sinusitis. Members **recommended** some education, potentially from $BPAC_{nz}$, to help prescribers determine the limited appropriate clinical circumstances for using oral cephalosporins in their patients. Members **recommended** the full funding of cefuroxime axetil if it were cost neutral to cefaclor.

1.4 The Subcommittee noted a request from a, Paediatric Infectious Disease Physician, for access to cephalexin oral liquid on practitioner supply order (PSO) for school based programs for use in group A streptococcal (GAS) sore throat as second-line if 'non-anaphylactic allergy' to beta lactams and possibly for use also in skin and soft tissue infections through school programmes. Members considered that increased use of cephalexin could result in increased rates of bacterial resistance. Members noted that the Sore Throat Guidelines were likely to be released for consultation in March 2014 and feedback would be sought from interested parties. Members deferred making a recommendation until the guideline review was complete.

1.5 The Subcommittee noted a request from the Heart Foundation of New Zealand for consideration of funding of clarithromycin oral liquid and tablets for treatment of GAS for beta lactam allergic patients. The Subcommittee noted that macrolide antibiotics were the first-line agent for GAS for patients with penicillin allergy. Members noted that the current macrolide, erythromycin, was an effective treatment but could frequently cause gastro-intestinal side effects. Members considered the request was regarding palatability rather than efficacy.

1.6 The Subcommittee considered that another macrolide, roxithromycin may not be appropriate for treatment of GAS as it does not effectively eradicate GAS. Moreover the Subcommittee noted that there is no dispersible nor liquid formulation of roxithromycin currently available in New Zealand for paediatric use. Members considered that both azithromycin and clarithromycin would be effective for treatment of GAS and there was no evidence that clarithromycin was more effective than azithromycin. Azithromycin is currently fully funded on the community schedule although members noted the comment from the Heart Foundation of New Zealand letter regarding its efforts to not widely recommend this in view of potential for inappropriate use. Members considered that if either of these treatment options was more widely available they would rapidly become a first-line agent, as people would resist using erythromycin due to its greater side effects.

1.7 Members noted that if the restriction on clarithromycin was widened under Special Authority to include GAS then this would require individual patient Special Authorities and would not be available on PSO. The Subcommittee **recommended** not widening the Special Authority for clarithromycin to include GAS eradication as a second-line macrolide at this time.

1.8 The Subcommittee considered a request from Southern DHB for cefazolin injections and probenecid to be included on PSO for treatment of cellulitis in the community. The Subcommittee considered that treating cellulitis in the community would be cost saving as patients would otherwise be admitted to hospital. Members noted that it was important that probenecid be available at the time of injection. Members **recommended** reducing barriers to access probenecid and cefazolin for treatment of cellulitis in the community, and considered that this may be improved by access via PSO. Members noted that it would be helpful to propose treatment duration, as patients should be being changed to oral treatment as soon as possible.

1.9 The Subcommittee noted the approvals for moxifloxacin by indication tabled by PHARMAC. Members noted a high prevalence of patients with impaired visual acuity (in the context of alternate treatments for tuberculosis) who access moxifloxacin and considered that this should be monitored.

1.10 The Subcommittee noted that the price of nystatin tablets and capsules had recently increased and PHARMAC had not increased the subsidy, so these products now have a part charge. Members considered that there

was no clinical requirement for nystatin tablets and capsules for the treatment of intestinal candidiasis. The Subcommittee considered there were no niche uses for nystatin tablets and capsules and **recommended** that they should be delisted as there was the potential for confusion with other treatments for oral candidiasis.

1.11 The Subcommittee noted the requests relating to wider access to lamivudine for prophylaxis of hepatitis B in patients who were undergoing immunosuppression. Members noted that methotrexate and related leflunomide are not associated with risk of HBsAg reactivation and that, according to current Special Authority criteria HBsAg positive patients on these therapies should not be treated with entecavir unless they have evidence of active chronic hepatitis B and already qualify for antiviral therapy. Members further noted that rituximab plus CHOP provides a high risk of reactivation in HBsAg negative, anti-HBcore positive patients because of the specific effect of anti-CD20 on humoral immunity combined with high dose steroids, which have a specific direct effect on HBV replication through activation of the glucocorticoid-responsive element on the HBV genome.

1.12 The Subcommittee noted a Named Patient Pharmaceutical Assessment (NPPA) application for tenofovir for a patient with chronic hepatitis B who wished to become pregnant. Members noted that there was a large amount of evidence for the safety of tenofovir due to the Antiretroviral Pregnancy Registry database (http://www.apregistry.com/forms/interim_report.pdf). Members noted that safety data for entecavir in pregnancy was lacking and that pre-clinical trials in rodents had suggested a higher risk of malignancy. Members note that current practice was to change a patient from entecavir to tenofovir on confirmation of pregnancy. Patients would then revert to entecavir following breastfeeding and then back to tenofovir for subsequent pregnancies.

1.13 The Subcommittee **recommended** that the Special Authority for tenofovir be amended to include women of child bearing potential, with a high priority.

1.14 The Subcommittee noted that patients were still being prescribed adefovir either alone or in combination with lamivudine. The Subcommittee noted that usage of adefovir was higher than anticipated following the availability of tenofovir for hepatitis B on the Pharmaceutical Schedule in December 2009, tenofovir being a both more effective and less expensive therapy. The Subcommittee considered that all patients on adefovir, with or without lamivudine, should be changed to tenofovir monotherapy and the Special Authority should be amended to ensure there was no barrier to access.

1.15 Members considered that all patients who could tolerate tenofovir should be transitioned to monotherapy with tenofovir as it was more efficacious and less expensive than the combination of adefovir plus lamivudine. The Subcommittee **recommended** amending the Special Authority to make

this easier for clinicians as follows (additions in **bold**, deletions in ~~strikethrough~~):

Initial application - (Chronic Hepatitis B) Only from a gastroenterologist, infectious disease specialist or general physician. Approvals valid without further renewal, unless notified, for applications meeting the following criteria:
Any of the following

1. Patient has confirmed Hepatitis B infection (HBsAg positive for more than 6 months); and
    1.1. All of the following
        1.1.1. Patient has had previous lamivudine, adefovir or entecavir therapy; and
        1.1.2. HBV DNA greater than 20,000 IU/mL or increased = 10 fold over nadir; and
        1.1.3. Any of the following:
            1.1.3.1. Lamivudine resistance - detection of M204I/V mutation; or
            1.1.3.2. Adefovir resistance - detection of A181T/V or N236T mutation; or
            1.1.3.3. Entecavir resistance - detection of relevant mutations including I169T, L180M T184S/A/I/L/G/C/M, S202C/G/I, M204V or M250I/V mutation; or
2. Patient is either listed or has undergone liver transplantation for HBV; or
3. Patient has decompensated cirrhosis with a Mayo score >20, **or**
4. **Patient is currently receiving adefovir therapy, or**
5. **Patient is a female of child bearing potential and is currently receiving entecavir; or**
6. **Patient is a female of child bearing potential and has confirmed Hepatitis B infection (HBsAg positive for more than 6 months); and**
    6.1 Either:
        6.1.1 ALT greater than upper limit of normal; or
        6.1.2 Severe fibrosis or cirrhosis on liver biopsy (Metavir stage $\geq$3 or 4) or on Fibroscan (LSM $\geq$ 8.0 kPa); and
    6.2 Either:
        6.2.1 HBeAg positive; or
        6.2.2 HBeAg negative and HBV DNA $\geq$ 2,000 IU HBV DNA units per ml

Initial application - (Pregnant, Active hepatitis B) only from a gastroenterologist, infectious disease physician or general physician. Approvals valid for 12 months for applications meeting the following criteria:
Both:

1 Patient is HBsAg positive and pregnant; and
2 HBV DNA > 20,000 IU/mL and ALT > ULN

Renewal - (Subsequent Pregnancy or Breastfeeding, Active hepatitis B) only from a gastroenterologist, infectious disease specialist or general physician. Approvals valid for 12 months for applications meeting the following criteria:
Both:

1 Patient is HBsAg positive and pregnant or breastfeeding; and
2 HBV DNA > 20,000 IU/mL and ALT > ULN

Initial application - (Pregnant, prevention of vertical transmission) only from a gastroenterologist, infectious disease specialist or general physician. Approvals valid for 6 months for applications meeting the following criteria:
Both:

1 Patient is HBsAg positive and pregnant; and
2 HBV DNA > 20,000 IU/mL and ALT > ULN

Renewal - (Subsequent Pregnancy, prevention of vertical transmission) only from a gastroenterologist, infectious disease specialist or general physician. Approvals valid for 6 months for applications meeting the following criteria:

Both:

1 Patient is HBsAg positive and pregnant; and
2 HBV DNA > 20,000 IU/mL and ALT > ULN

1.16 The Subcommittee noted that valaciclovir had been included in the 2011/12 Tender and that this tender was currently unresolved. Members considered that if the Special Authority restriction was removed from valaciclovir that the majority of patients would be transferred from aciclovir to valaciclovir, as valaciclovir had better bioavailability and a less frequent dosing regimen which may improve compliance.

1.17 Members considered that there would be no clinical requirement to fund the 250 mg or 1000 mg valaciclovir tablets, however if there was no cost differential the 1000 mg tablet would reduce tablet burden for patients requiring a higher dose. Members noted that valaciclovir would potentially reduce the duration of post herpetic neuralgia following shingles if it replaced aciclovir.

1.18 Subcommittee noted that there was an ongoing requirement for oral acyclovir for use in very young infants. Members noted this is used for secondary prevention in the community after severe neonatal herpes for at least 6 months. The role of valaciclovir has not as yet been evaluated in this context therefore it cannot completely replace oral acyclovir at this stage.

1.19 The Subcommittee considered that there would be clinical benefits in removing the Special Authority restrictions on valaciclovir and, provided costs to the health sector were acceptable, **recommended** removing the restriction with a medium priority.

1.20 The Subcommittee considered the current Special Authority for antiretrovirals. The Subcommittee noted that the major impediment for initiating a patient on therapy would be compliance concerns, and that very few new patients (less than 5% increase in new patients over status quo) would be initiated on therapy if the CD4 count requirement was removed. Members noted that the Special Authority required a Named Antiretroviral Specialist to apply for funding, and considered this would ensure only appropriate patients would be initiated on therapy in the New Zealand setting.

1.21 The Subcommittee **recommended** amending the Special Authority relating to antiretrovirals with a medium priority as follows (additions in **bold**, deletions in ~~strikethrough~~):

Initial application - (Confirmed HIV/AIDS) only from a named specialist. Approvals valid without further renewal unless notified for applications ~~meeting the following criteria:~~
~~Both:~~
~~1~~ **where the patient has c**onfirmed HIV infection.~~ and~~
~~2 Any of the following:~~
~~2.1 Symptomatic patient; or~~
~~2.2 Patient aged 12 months and under; or~~
~~2.3 Both:~~
~~2.3.1 Patient aged 1 to 5 years; and~~
~~2.3.2 Any of the following:~~

~~2.3.2.1 CD4 counts < 1,000 cells/mm^3~~
~~2.3.2.2 CD4 counts < 0.25 × total lymphocyte count~~
~~2.3.2.3 Viral load counts > 100,000 copies per ml; or~~
~~2.4 Both:~~
~~2.4.1 Patient aged 6 years and over; and~~
~~2.4.2 CD4 counts < 500 cells/mm^3~~

1.22 The Subcommittee reviewed a summary of the NPPA applications and considered that there did not appear to be any applications that should be considered for schedule listing at this time.

2 Ceftaroline fosamil for complicated Skin and Soft Tissue Infections (cSSTI) and Community- Acquired Pneumonia (CAP) in adults

2.1 The Subcommittee noted that PHARMAC has received an application from AstraZeneca for the listing of ceftaroline fosamil in section H of the Pharmaceutical Schedule for the following infections:

- Complicated skin and soft tissue infections (cSSTI)
- Community- acquired Pneumonia (CAP)

2.2 The Subcommittee noted that the supplier proposed that prescribing of ceftaroline fosamil be restricted to Infectious Disease Physicians or Clinical Microbiologists. Members noted that the proposed use is for the treatment of hospitalised patients.

2.3 The Subcommittee noted that the application has not been considered by PTAC, and that PHARMAC was seeking the advice of the Subcommittee prior to review of the application by PTAC in May.

2.4 The Subcommittee noted that ceftaroline fosamil is the pro-drug of ceftaroline, which is an extended-spectrum cephalosporin that exhibits time-dependent bactericidal activity against numerous Gram-negative and Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*.

2.5 The subcommittee noted that in vitro studies have shown that ceftaroline fosamil inhibits bacterial cell wall synthesis in methicillin-resistant *S. aureus* (MRSA) and penicillin non-susceptible *S. pneumoniae* (PNSP) due to its affinity for the altered penicillin binding proteins (PBPs) found in these organisms.

2.6 The Subcommittee noted that for the treatment of cSSTI and CAP, the recommended dose of ceftaroline fosamil is 600 mg administered every 12 hours by intravenous infusion over 60 minutes in patients aged 18 years or older. Members noted that the recommended treatment duration for cSSTI is 5 to 14 days and the recommended duration of treatment for CAP is 5 to 7 days.

2.7 The Subcommittee noted that the excretion of ceftaroline fosamil is mainly renal and there is therefore a requirement for dose adjustments in patients with impaired renal function.

2.8 The Subcommittee noted that parenteral cephalosporins have been associated with gastrointestinal disturbances such as nausea, vomiting, and diarrhoea. The Subcommittee noted that approximately 5% of patients who received ceftaroline fosamil in phase three studies developed diarrhoea and 3% developed a rash. Members noted that two case reports of eosinophilic pneumonia and one case report of neutropenia have also been observed with ceftaroline fosamil.

2.9 The Subcommittee noted that ceftaroline fosamil is active *in vitro* against Gram-positive cocci, including MRSA, methicillin-resistant coagulase-negative staphylococci, penicillin-resistant *S. pneumoniae* and has some activity against vancomycin-resistant *Enterococcus faecalis* (but not *E. faecium*). Members noted that the broad-spectrum activity of ceftaroline fosamil includes many Gram-negative pathogens but does not extend to extended-spectrum beta-lactamase-producing or AmpC-derepressed Enterobacteriaceae or most nonfermentative Gram-negative bacilli including *Pseudomonas aeruginosa*. Members noted that ceftaroline fosamil demonstrates limited activity against anaerobes such as *Bacteroides fragilis* and non-fragilis *Bacteroides* spp.

2.10 The Subcommittee noted the four pivotal trials where ceftaroline fosamil has been studied for the treatment of complicated skin and skin structure infections (cSSTI) and community-acquired pneumonia (CAP) in phase III randomised, double-blind, international, multicentre non-inferiority clinical trials (Corey GR et al. J Antimicrob Chemother. 2010; 65 [CANVAS 1]; Wilcox et al. Antimicrob Chemother. 2010;65 [CANVAS 2]; File et al. J Antimicrob Chemother. 2011;66 Suppl 3 [FOCUS 1]; Low et al. J Antimicrobl Chemother. 2011;66 [FOCUS 2]).

2.11 The Subcommittee noted that the CANVAS studies determined non-inferiority of ceftaroline fosamil for the treatment of adults with complicated skin and skin structure infections cSSSIs. Adult patients with cSSSIs requiring intravenous therapy were randomised to receive 600 mg of ceftaroline fosamil 12 hourly or 1 g of vancomycin plus 1 g of aztreonam 12 hourly for 5 to 14 days. The Subcommittee noted that in New Zealand flucloxacillin or clindamycin, rather than vancomycin or aztreonam, is used in the treatment of cSSSIs.

2.12 The Subcommittee noted that the FOCUS trials determined non-inferiority in clinical cure rates achieved with ceftaroline fosamil compared with those achieved with ceftriaxone in the clinically evaluable (CE) and modified intent-to-treat efficacy (MITTE) populations. The patients were randomised to receive either 600 mg of ceftaroline fosamil IV 12 hourly or 1 g of ceftriaxone IV every 24 hours. The Subcommittee considered that in New Zealand ceftriaxone is not routinely used in CAP and the ceftriaxone dose used in the trial was slightly low in the context of *S pneumoniae*

betalactam resistance and that amoxicillin and amoxicillin and clavulanic acid is more likely to be used in CAP.

2.13 The Subcommittee noted that there were three case reports related to the use of ceftaroline fosamil in treatment of severe MRSA infections. Members considered that further comparative studies are needed for the use of ceftaroline fosamil in severe MRSA infections.

2.14 The Subcommittee considered that, based on minimum inhibitory concentration (MIC) testing, ceftaroline fosamil was much more effective than ceftriaxone for pneumococci.

2.15 The Subcommittee considered that, despite concerns, clindamycin or vancomycin continue to be the standard treatment for severe skin and soft tissue infections when β-lactam antimicrobials cannot be used. Members noted there is no paediatric dosing data or study on ceftaroline, and children are a group with high rates of cSSi. The Subcommittee considered that there is currently no role for ceftaroline fosamil for cSSSi in this country due to the effectiveness of the range of funded agents currently available

2.16 The Subcommittee noted that CAP is generally treated with erythromycin and a β-lactam. The Subcommittee considered that ceftaroline fosamil may have a place in CAP as salvage therapy but that it had no role as first-line therapy of CAP.

2.17 The Subcommittee considered that there may be a role for ceftaroline fosamil in MRSA bacteraemia, endocarditis, and deep seated infections or penicillin resistant pneumococcal pneumonia/meningitis. Members noted these indications to be very different from the four clinical trials that have formed the basis of registration of this product. The Subcommittee considered that 20 cases per year might present with these serious indications. The Subcommittee considered that there was a need for more evidence for ceftaroline fosamil in these settings.

2.18 The Subcommittee **recommended** listing ceftaroline fosamil with a medium priority in section H of the Pharmaceutical Schedule for multi-resistant organisms salvage therapy for patients where alternative therapies have failed or who have a contraindication or hypersensitivity to standard current therapies, and only on the recommendation of an Infectious Disease Physician or Clinical Microbiologist

3 Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis

3.1 The Subcommittee noted an application from a Clinician, requesting funding of azithromycin for the prevention of exacerbations in non-cystic fibrosis bronchiectasis in patients who have had at least one lung infection in the previous year.

3.2 The Subcommittee noted that bronchiectasis is a mostly progressive lung condition with up to 75% due to previous severe respiratory infection or of unknown aetiology. Members noted that this was a disease associated with low socioeconomic status. Members noted that there was also a high childhood incidence particularly in Maori and Pacific Island children.

3.3 A member noted a retrospective review of bronchiectasis cases over one calendar year at Counties Manukau District Health Board (CMDHB) of patients aged 15 years and over (Roberts et al. Intern Med J. 2012;42(6):e129-36). 243 patients (with 438 admissions) with bronchiectasis on coding were identified, of whom 152 patients (with 307 admissions) were confirmed as primary cause of admission due to bronchiectasis exacerbation. 27% were Maori and 44% Pacific Island. 32 patients died within 12 months of admission, giving a 12 month all-cause mortality of 21% in those with hospital admission.

3.4 A member noted a review by Byrnes & Trenholme (J Paediatr Child Health. 2010;46(9):521-6) of respiratory infections in New Zealand children and young people. The paper reported the New Zealand annual incidence of new paediatric bronchiectasis diagnoses of 3.7 per 100,000 per year, being 7 to 18 times higher than other developed countries. The paper also noted that the disease described in children at presentation in New Zealand is more severe than elsewhere, with lungs affected bilaterally in 80-90%; and with 60% of cases affecting 4 or more lobes.

3.5 The Subcommittee considered that it was inappropriate to review long term macrolides for non CF bronchiectasis without the consideration of paediatric infection and whether therapy would be accessible to both adults and children.

3.6 The Subcommittee noted four good quality randomised controlled trials investigating using macrolides as prophylaxis for non CF bronchiectasis, three investigating azithromycin and one using erythromycin, and three of the four performed in Australian and/or New Zealand patient cohorts.

3.7 The EMBRACE trial (Wong et al. Lancet 2012,118:380,660-7) was a randomised double blind trial undertaken in three centres in New Zealand comparing azithromycin vs placebo at a dose of 500 mg three times a week for a period of 6 months. The patient population investigated was adults aged 18 years and over with non CF bronchiectasis diagnosed by high resolution CT scan. Patients had experienced 3 to 4 median exacerbations in the previous year. There was a statistically significant reduction in the number of event-based exacerbations in the azithromycin group compared with placebo; however there were no statistically significant differences in changes in FEV_1 or quality of life between the two groups although the study was not powered to detect a true clinically significant difference in QO (via St George's respiratory questionnaire). The impact of resistance was not reported.

3.8 Altenburg et al (JAMA. 2013.;309:1251-9) reported a randomised double blind trial of 83 non CF bronchiectasis adults who had 3 or more lower

respiratory tract infections in the previous year. Patients were randomised to either azithromycin 250 mg daily (43 patients) or placebo (40 patients) for 12 months. There was a statistically significant reduction in the number of exacerbations in the azithromycin group compared to placebo.

3.9 Serisier et al (JAMA. 2013;309) reported results of the BLESS trial, a randomised double blind trial comparing low dose erythromycin vs placebo in adults with non CF bronchiectasis with a history of 2 or more exacerbation in the preceding year. Patients were randomised to receive either erythromycin ethyl succinate 400 mg twice daily (58 patients) or placebo (59 patients). There was a statistically significant reduction in the number of exacerbations in the erythromycin group compared to placebo. The trial also reported a statistically significant increase in macrolide-resistant oropharyngeal streptococci in patients receiving erythromycin compared to the placebo arm.

3.10 Valery et al (Lancet Respir Med. 2013;1:610-20) reported a randomised double blind trial comparing azithromycin (30 mg/kg) (45 patients) once weekly or placebo (44 patients) once weekly for up to 24 months. The patient population investigated was indigenous Australian, Maori, and Pacific Island children aged 1-8 years with either bronchiectasis or chronic suppurative lung disease. Patients had experienced at least one pulmonary exacerbation in the previous 12 months. Once-weekly azithromycin for up to 24 months resulted in a statistically significant decrease in pulmonary exacerbations in indigenous children with non-cystic-fibrosis bronchiectasis or chronic suppurative lung disease. The study reported significantly increased carriage of azithromycin-resistant bacteria in those in the treatment group, affecting close to half patients receiving azithromycin.

3.11 Members noted that the studies supported the use of macrolides in reducing exacerbations, but varying clinically meaningful improvements in the measured quality of life were demonstrated. Members noted that there was a measured increase in carriage of resistant microbes and that this could have an impact on the treatment of other infections in these patients and in the transmission of resistance in the community, potentially amongst a population of adults and children with high rates of other infectious disease. Members noted that the follow up were relatively of short duration at this stage without evidence of life extension as a result of the intervention.

3.12 Members noted the Thoracic Society of Australia and New Zealand position statement of 2010 regarding management for bronchiectasis in adults and children. This stated that long term oral antibiotics (greater than 1 month and less than 24 months) should not be considered routinely. The statement considers that in selected patients with frequent exacerbations (>6) and/or hospitalisations (>2) over 12 months or more than 6 months continuous symptoms may benefit from a trial of a long term antibiotic. Members noted that the position statement was currently under review and may eventually give less conservative recommendations regarding macrolides, based on the recent papers reviewed above.

3.13 The Subcommittee noted four papers on the macrolide class effect on resistance (Malhotra-Kumar S et al. Lancet. 2007;369(9560):482-490; Kastner & Guggenbichler. Infection. 2001;29(5):251-256; Barkai G et al. Emerg Infect Dis. 2005;11(6):829-837; Dias & Canic¸a. J Antimicrob Chemother. 2004;54(6):1035-1039.). Members noted that all macrolides would cause an increase in antimicrobial resistance in patients. However, azithromycin may cause higher level of resistant organisms which persisted for a longer period of time. Members considered that this could result in greater transmission of resistant organisms in the wider community.

3.14 Members noted that there were potential adverse effects that should be considered prior to initiating long term macrolide therapy, namely impacts on hearing, liver function and QT prolongation. Members noted that prior to therapy being initiated patients should undergo baseline ECG, hearing and liver function.

3.15 The Subcommittee noted that erythromycin ethyl succinate was funded without restriction and could be used in patients for this indication. Members noted that evidence supporting one macrolide over another at this time is still incomplete. Members considered it was not clear at this stage what treatment duration or macrolide dosage or which group may get most benefit (for example young children, older adults, number of exacerbations >3 in prior 6 months). The Subcommittee **recommended** presenting a paper to the Respiratory Subcommittee of PTAC regarding the use of macrolides in this paediatric and adult bronchiectasis patient population.

3.16 The Subcommittee **recommended** PHARMAC staff present a paper with minutes from the Respiratory Subcommittee and if available, the updated Thoracic Society of Australia and New Zealand position statement at the next Anti-Infective Subcommittee meeting to allow further review.