

Anti-Infective Subcommittee of PTAC

Meeting held 1 December 2014

(minutes for web publishing)

Anti-Infective Subcommittee 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 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 on 7 & 8 May 2015, a record of which will be available in July 2015.

Record of the Anti-Infective Subcommittee of the Pharmacology and Therapeutics Committee (PTAC) meeting held at PHARMAC on 1 December 2014

1 Community therapeutic group review

Ribavirin for respiratory syncytial virus (RSV)

- 1.5 The Subcommittee noted correspondence a DHB Hospital Pharmacist questioning whether ribavirin has been considered by PTAC for listing on the Hospital Medicines List for the treatment of RSV. The pharmacist noted that the testing for influenza now included reporting on RSV infection and that this would likely increase the detection of RSV. The Subcommittee noted that ribavirin is not currently listed on the HML, nor has it been reviewed by PTAC for RSV infection. The Subcommittee noted previous correspondence had been received from the Paediatric Society and Starship subspecialists in 2013 about the issue of ribavirin availability. The Subcommittee considered whether ribavirin should be listed on the Hospital Medicines List for patients with RSV infection.
- 1.6 The Subcommittee noted a review article by Shah and Chemaly (Blood. 2011; 117(10):2755-63) on the management of RSV infections in adult recipients of haemopoietic stem cell transplant (HSCT). The Subcommittee noted that ribavirin was available in aerosol, IV and oral formulations and is used either alone or in combination with an immunomodulator (intravenous immunoglobulin). The Subcommittee noted that most of the studies contained in the review used an aerosol formulation and there were fewer studies on oral and IV formulations. The Subcommittee noted that the nebulised formulation was delivered by continuous nebulization with a Small Particle Aerosol Generator. The Subcommittee noted that the most effective regime with regard to progression to lower respiratory tract infection and mortality was aerosol ribavirin with immunomodulator. The Subcommittee noted the papers' recommendations; to treat HSCT patients who have at least one identifiable risk factor for progression of lower respiratory tract infection promptly with nebulised or oral ribavirin, to treat HSCT patients with established RSV lower respiratory tract infection with nebulised ribavirin and in combination with an immunomodulator and that HSCT patients with multiple risk factors should be considered for treatment with ribavirin in combination with an immunomodulator. The Subcommittee noted the limitations of the studies included small sample sizes, a lack of randomised controlled trials, that sicker patients were selected for treatment, that there were a lack of guidelines on standard treatment regimens and length of treatment and a number of patients had concurrent infections.
- 1.7 The Subcommittee noted a literature review by a working group of the Fourth European Conference on Infections in Leukaemia on community-acquired respiratory infections, including RSV, in patients with leukaemia and those undergoing hematopoietic stem cell transplantation (Hirsch et al. Clin Infect Dis. 2013;56(2):258-66). The Subcommittee noted that the pooling of published studies suggested that treating upper respiratory tract infection in leukaemia patients undergoing HSCT who are at risk for lower respiratory tract infection, and treating manifest lower respiratory tract infection with ribavirin and

intravenous immunoglobulin improved outcomes. The Subcommittee noted that for allogenic HSCT patients with RSV lower respiratory tract infection or at high risk for RSV lower respiratory tract infection, nebulized or systemic ribavirin therapy could be combined with intravenous immunoglobulin or anti-RSV-enriched antibody preparations. The Subcommittee also noted that proper meta-analyses were not possible, and the results should be interpreted with caution. The Subcommittee noted the author's conclusion that there is limited evidence for effective treatments because of the lack of potent antiviral drugs and sufficiently powered, randomised controlled clinical trials.

- 1.8 Overall the Subcommittee considered that the level of evidence was low and that there is limited data on the oral formulation of ribavirin.
- 1.9 The Subcommittee noted the various dosing regimens for ribavirin in HSCT patients; the continuous regimen constitutes administration of 6 g of nebulised ribavirin over 18 hours for 5 to 7 days, and the intermittent regimen requires administration of 2 g of nebulised ribavirin over 2 to 3 hours every 8 hours for 5 to 7 days. The Subcommittee noted that systemic ribavirin can be administered orally or intravenously as 10-30mg/kg body weight in 3 divided doses.
- 1.10 The Subcommittee noted that the equipment required to deliver nebulised ribavirin is specialised and can be difficult to access. The Subcommittee considered that access to this equipment would be limited in DHBs in New Zealand which would limit treatment options.
- 1.11 The Subcommittee considered ribavirin should be available for use for severely immunocompromised patients with symptomatic proven RSV infection who are at high risk of life threatening RSV lower respiratory tract infection or who have established RSV lower respiratory tract infection.
- 1.12 The Subcommittee **recommended** that oral, intravenous and nebulised ribavirin should be listed on Part II of Section H of the Pharmaceutical Schedule (the Hospital Medicines List) as follows:

Restricted

1. Either
 - 1.1. Patient is severely immunocompromised and has established RSV lower respiratory tract infection; or
 - 1.2. Patient is severely immunocompromised with symptomatic, proven RSV infection and is at high risk of RSV lower respiratory tract infection; or
 - 1.3. Patient has complicated measles (e.g encephalitis).

Norflloxacin

- 1.13 The Subcommittee noted correspondence from a Pharmacist seeking clarification with regard to the norflloxacin restriction in the Pharmaceutical Schedule.

- 1.14 The Subcommittee noted that currently norfloxacin can be fully subsidised in the community if the prescription meets the following subsidy by endorsement requirement:

Only if prescribed for a patient with an uncomplicated urinary tract infection that is unresponsive to a first line agent or with proven resistance to first line agents and the prescription is endorsed accordingly.

- 1.15 The Subcommittee noted that BPAC's advice is in relation to norfloxacin is ambiguous stating norfloxacin should be used as second line agent for uncomplicated urinary tract infection in the BPAC antibiotic handbook, but in a later 2013 article considered that it should be a third line agent.
- 1.16 The Subcommittee considered that the intent of the restriction on norfloxacin was to limit norfloxacin as a third line agent in uncomplicated urinary tract infections if the infection is unresponsive or resistant to both trimethoprim and nitrofurantoin. The Subcommittee considered that the current subsidy by endorsement requirement should be amended to more accurately reflect the intent of the restriction.
- 1.17 The Subcommittee noted that modified release nitrofurantoin has been included in the 2014/15 Invitation to Tender. The Subcommittee considered that if a modified release nitrofurantoin was available, allowing twice daily dosing, this could be an advantage over current four times a day dosing and could aid compliance and possibly reduce adverse events.

Roxithromycin dispersible tablets

- 1.18 The Subcommittee noted correspondence to PHARMAC from a Paediatric Infectious Diseases Physician regarding access to roxithromycin dispersible tablets to enable children to have access to a new generation macrolide for group A beta-haemolytic streptococcus (GAS) pharyngitis.
- 1.19 The Subcommittee noted that at its previous meeting of 26 February 2014, it considered a number of treatments for GAS. At that meeting, the Subcommittee recommended that a request for widening of funding of clarithromycin oral liquid for GAS eradication be declined noting that it would require individual patient Special Authorities to be issued and would not be available on a Practitioner Supply Order. At that meeting the Subcommittee also noted that erythromycin was an effective treatment for GAS but could be limited by gastrointestinal adverse events. The Subcommittee also noted its previous discussion that roxithromycin may not be appropriate for treatment of GAS as it does not effectively eradicate GAS.
- 1.20 The Subcommittee noted that access to roxithromycin dispersible tablets would assist in avoiding use of azithromycin elixir, which is considered to induce antimicrobial resistance and as a long acting macrolide this may be more likely to induce resistance than other macrolides. The Subcommittee also noted that the correspondent acknowledged that evidence for use of roxithromycin for GAS is not strong and that although the literature summary for roxithromycin in GAS is adequate, it is not high quality. The Subcommittee considered that given dosing advantage of roxithromycin over erythromycin and lower gastrointestinal side

- effect profile, roxithromycin would likely improve compliance and outcomes in GAS eradication if available
- 1.21 The Subcommittee considered that access to roxithromycin dispersible tablets would be particularly beneficial for children with penicillin allergy and intolerance to erythromycin. The Subcommittee considered that roxithromycin dispersible tablets would be useful for the treatment of other indications and should not be limited to patients with GAS.
- 1.22 The Subcommittee noted that the dosing equivalence for full dose roxithromycin was 300mg daily compared to 1600mg daily of erythromycin ethyl succinate. The Subcommittee also noted that the New Zealand Formulary for Children (NZFC) states the roxithromycin dose for patients <40kg as 2.5-4mg/kg twice daily, and in patients >40kg as 150mg twice daily. The Subcommittee noted that the NZFC states the dose of erythromycin to be 20-25mg/kg twice daily. The Subcommittee considered that this suggests that roxithromycin was 5-10 times the potency of erythromycin on a mg to mg basis.
- 1.23 The Subcommittee **recommended** roxithromycin dispersible tablets be listed on the Pharmaceutical Schedule without restriction with a high priority. The Subcommittee **recommended** that the provision of education in this area would be useful to ensure appropriate use of treatment.

Clindamycin for penicillin-allergic dental patients

- 1.24 The Subcommittee noted correspondence and references provided by a Dental Surgeon requesting PHARMAC to widen access to clindamycin for treatment of serious dental infections in patients allergic to penicillin when prescribed by a dentist or dental specialist.
- 1.25 The Subcommittee noted that a number of alternative treatments for penicillin allergic patients with serious dental infection are available including cephalosporins, macrolides, tetracyclines, metronidazole, as well as clindamycin. The Subcommittee noted that currently there are no issues in access to these alternative treatments. The Subcommittee noted that although some studies suggested clindamycin as a second-line treatment in penicillin-allergic patients, other antibiotics were also considered as suitable second-line agents including metronidazole, erythromycin and cephalexin. The Subcommittee noted that there was currently sufficient access to alternative antibiotics for penicillin allergic patients with serious dental infections and there was no evidence presented to ascertain comparable efficacy between clindamycin and alternative antibiotics.
- 1.26 The Subcommittee noted concern at the increasing resistance rates to antibiotics other than penicillin, especially macrolides and clindamycin.
- 1.27 The Subcommittee **recommended** that access to clindamycin is not widened for the treatment of serious dental infections in patients allergic to penicillin.

Paromomycin

- 1.28 The Subcommittee noted a funding application received from an Infectious Diseases Physician regarding access to paromomycin, diloxanide or iodoquinol in the community for the treatment of *Entamoeba histolytic* carriage. The Subcommittee noted that currently diloxanide and iodoquinol are not listed on the Pharmaceutical Schedule. The Subcommittee noted that paromomycin is currently listed on Section B of the Pharmaceutical Schedule under the following Special Authority:

Initial application only from an infectious disease specialist or clinical microbiologist. Approvals valid for 1 month where the patient has confirmed cryptosporidium infection.

Renewal only from an infectious disease specialist or clinical microbiologist. Approvals valid for 1 month where the patient has confirmed cryptosporidium infection.

- 1.29 The Subcommittee noted that PHARMAC has received eight previous NPPA applications for paromomycin or diloxanide for treatment of *Entamoeba histolytica* carriage in the bowel. The Subcommittee considered that there is an unmet health need and that benefits of treatment of *Entamoeba histolytica* carriage in the bowel would include eradication of carriage, avoidance of liver abscess and potential avoidance of transmission. The Subcommittee considered that 10-20 patients would require access to treatment for this indication per annum.

- 1.30 The Subcommittee **recommended** that the current restriction for paromomycin be changed as follows with a high priority (additions in bold, deletions in strike through):

Initial application only from an infectious disease specialist or clinical microbiologist. Approvals valid for 1 month where the patient has confirmed cryptosporidium infection **or for the eradication of *E.histolytica* carriage.**

Renewal only from an infectious disease specialist or clinical microbiologist. Approvals valid for 1 month where the patient has confirmed cryptosporidium infection **or for the eradication of *E.histolytica* carriage.**

Primaquine

- 1.31 The Subcommittee noted that PHARMAC had received correspondence from an Infectious Disease Physician regarding access to primaquine phosphate for the treatment of *Plasmodium vivax* malaria. The correspondent noted that approximately 10% of patients would require two or more courses of primaquine to clear the infection.
- 1.32 The Subcommittee noted that primaquine phosphate is currently listed on Section B of the Pharmaceutical Schedule under the following Special Authority. The Subcommittee noted that currently there is no ability to renew an approved Special Authority:

Initial application only from an infectious disease specialist or clinical microbiologist. Approvals valid for 1 month for applications meeting the following criteria:

Both:

- 1 The patient has vivax or ovale malaria; and
- 2 Primaquine is to be given for a maximum of 21 days

- 1.33 The Subcommittee noted that there is a 10-13% relapse rate following treatment for *Plasmodium vivax* malaria. The Subcommittee noted that there was little difference in success rates between different treatment durations.
- 1.34 The Subcommittee noted that the recommended dose of primaquine phosphate is 15mg - 30mg.
- 1.35 The Subcommittee **recommended** that renewal criteria for subsequent courses of primaquine phosphate be added to the Special Authority as follows (additions in bold, deletions in strike through):

Initial application only from an infectious disease specialist or clinical microbiologist. Approvals valid for 1 month for applications meeting the following criteria:

Both:

- 1 The patient has vivax or ovale malaria; and
- 2 Primaquine is to be given for a maximum of 21 days

Renewal only from an infectious disease specialist or clinical microbiologist. Approvals valid for 1 month for applications meeting the following criteria:

Both:

- 1 The patient has relapsed vivax or ovale malaria; and**
- 2 Primaquine is to be given for a maximum of 21 days**

Minocycline hydrochloride

- 1.36 The Subcommittee noted a request from PHARMAC for advice as to the relative risk of systemic lupus erythematosus (SLE) associated with the use of minocycline and whether this would be a reason to restrict access to this treatment. The Subcommittee noted that minocycline can be used in the treatment of acne and it is currently listed on Section B of the Pharmaceutical Schedule for rosacea.
- 1.37 The Subcommittee noted that the rates of SLE associated with minocycline appeared to be low. The Subcommittee noted that hepatitis can result from minocycline treatment. The Subcommittee noted this can either present early as a result of hypersensitivity or after chronic treatment as an autoimmune response.
- 1.38 The Subcommittee noted that low dose doxycycline can also be used for the treatment of acne (25–40 mg daily). The Subcommittee considered that the efficacy of low dose doxycycline and minocycline are similar. The Subcommittee considered that while minocycline may have a faster effect, low dose doxycycline has fewer side effects. The Subcommittee questioned whether low dose doxycycline would increase risk of resistance.
- 1.39 The Subcommittee **recommended** that advice should be sought from the Dermatological Subcommittee of PTAC on the optimal treatments for rosacea and acne.

Lamivudine

- 1.40 The Subcommittee noted that PHARMAC has received NPPA applications for funding of lamivudine for prevention of reactivation of hepatitis B in patients who meet the entry criteria for funding, but are having a subsequent immunosuppression, or treatment for longer than 12 months. The Subcommittee noted that under the current renewal criteria these patients would not have access to further courses of lamivudine treatment to prevent reactivation of hepatitis B.
- 1.41 The Subcommittee noted that tenofovir is now fully subsidised for those patients who has exhibited resistance to lamivudine or adefovir therapy. The Subcommittee noted that tenofovir monotherapy has been demonstrated to be safe and effective for treatment of patients with lamivudine-resistant, chronic hepatitis B infection (Fung et al. Gastroenterology 2014;146:980–988, Corsa et al. Clinical Gastroenterology and Hepatology 2014;12:2106–2112, Berg et al. Journal of Hepatology 2014 vol. 60 715–722) .
- 1.42 The Subcommittee **recommended** that the renewal criteria for lamivudine in Section B of the Pharmaceutical Schedule should be amended as follows (additions in bold, deletions in strike through):

Renewal (**other indications**) only from a gastroenterologist, infectious disease specialist, paediatrician, general physician or medical practitioner on the recommendation of a gastroenterologist, infectious disease specialist, paediatrician or general physician. Approvals valid for 2 years for applications meeting the following criteria:

Any of the following:

Renewal for patients who have maintained continuous treatment and response to lamivudine

1 All of the following:

- 1.1 Have maintained continuous treatment with lamivudine; and
- 1.2 Most recent test result shows continuing biochemical response (normal ALT); and
- 1.3 HBV DNA <100,000 copies per ml by quantitative PCR at a reference laboratory.;

~~Renewal when given in combination with adefovir dipivoxil for patients with cirrhosis and resistance to lamivudine~~

~~2 All of the following:~~

- ~~2.1 Lamivudine to be used in combination with adefovir dipivoxil; and~~
- ~~2.2 Patient is cirrhotic; and~~
- ~~Documented resistance to lamivudine, defined as:~~
- ~~2.3 Patient has raised serum ALT (> 1 x ULN); and~~
- ~~2.4 Patient has HBV DNA greater than 100,000 copies per mL, or viral load = 10 fold over nadir; and~~
- ~~2.5 Detection of M204I or M204V mutation; or~~

~~Renewal when given in combination with adefovir dipivoxil for patients with resistance to adefovir dipivoxil~~

~~3 All of the following:~~

- ~~3.1 Lamivudine to be used in combination with adefovir dipivoxil; and~~
- ~~Documented resistance to adefovir, defined as:~~
- ~~3.2 Patient has raised serum ALT (> 1 x ULN); and~~
- ~~3.3 Patient has HBV DNA greater than 100,000 copies per mL, or viral load = 10 fold over nadir; and~~
- ~~3.4 Detection of N236T or A181T/V mutation.~~

Renewal – (subsequent immunosuppression or immunosuppression for duration over 1 year) application only from a gastroenterologist, infectious disease specialist, paediatrician

or general physician or on the recommendation of a gastroenterologist, infectious disease specialist, paediatrician or general physician. Approvals valid for 1 year for applications meeting the following criteria:

Any of the following:

- 1 HBV DNA positive cirrhosis prior to liver transplantation; or
- 2 HBsAg positive and have had a liver, kidney, heart, lung or bone marrow transplant; or
- 3 Hepatitis B virus naïve patient who has received a liver transplant from an anti-HBc (Hepatitis B core antibody) positive donor; or
- 4 Hepatitis B surface antigen (HbsAg) positive patient who is receiving chemotherapy for a malignancy, or high dose steroids (at least 20mg/day for at least 7 days) or who has received such treatment within the previous two months; or
- 5 Hepatitis B surface antigen positive patient who is receiving anti-tumour necrosis factor treatment; or
- 6 Hepatitis B core antibody (anti-HBc) positive patient who is receiving rituximab plus high dose steroids (e.g. R-CHOP).

- 1.43 The Subcommittee **recommended** that the continuation restriction criteria for lamivudine in Part II of Section H of the Pharmaceutical Schedule should be amended as follows (additions in bold, deletions in strike through):

Restricted

Gastroenterologist, infectious disease specialist, paediatrician or general physician

Continuation - patients who have maintained continuous treatment and response to lamivudine
Re-assessment required after 2 years

All of the following:

- 1 Have maintained continuous treatment with lamivudine; and
- 2 Most recent test result shows continuing biochemical response (normal ALT); and
- 3 HBV DNA <100,000 copies per ml by quantitative PCR at a reference laboratory; or

~~Continuation - when given in combination with adefovir dipivoxil for patients with cirrhosis and resistance to lamivudine~~

~~Re-assessment required after 2 years~~

~~All of the following:~~

- ~~1 Lamivudine to be used in combination with adefovir dipivoxil; and~~
- ~~2 Patient is cirrhotic; and~~

~~Documented resistance to lamivudine, defined as:~~

- ~~1 Patient has raised serum ALT (> 1 ULN); and~~
- ~~2 Patient has HBV DNA greater than 100,000 copies per mL, or viral load 10 fold over nadir; and~~
- ~~3 Detection of M204I or M204V mutation; or~~

~~Continuation - when given in combination with adefovir dipivoxil for patients with resistance to adefovir dipivoxil~~

~~Re-assessment required after 2 years~~

~~All of the following:~~

- ~~1 Lamivudine to be used in combination with adefovir dipivoxil; and~~

~~2 Documented resistance to adefovir, defined as:~~

- ~~a) 1 Patient has raised serum ALT (> 1 ULN); and~~
- ~~b) 2 Patient has HBV DNA greater than 100,000 copies per mL, or viral load 10 fold over nadir; and~~
- ~~c) Detection of N236T or A181T/V mutation.~~

Continuation - subsequent immunosuppression or immunosuppression for duration over 1 year

Re-assessment required after 1 year

Any of the following:

- 1 HBV DNA positive cirrhosis prior to liver transplantation; or
- 2 HBsAg positive and have had a liver, kidney, heart, lung or bone marrow transplant; or
- 3 Hepatitis B virus naïve patient who has received a liver transplant from an anti-HBc (Hepatitis B core antibody) positive donor; or

- 4 Hepatitis B surface antigen (HbsAg) positive patient who is receiving chemotherapy for a malignancy, or high dose steroids (at least 20mg/day for at least 7 days) or who has received such treatment within the previous two months; or
- 5 Hepatitis B surface antigen positive patient who is receiving anti-tumour necrosis factor treatment; or
- 6 Hepatitis B core antibody (anti-HBc) positive patient who is receiving rituximab plus high dose steroids (e.g. R-CHOP).

Tobramycin

- 1.50 The Subcommittee noted the NPPA applications for pharmaceuticals that fall within the infections Therapeutic Group that have been received by PHARMAC since the last Subcommittee meeting.
- 1.51 The Subcommittee noted a number of NPPA applications for tobramycin for bronchiectasis. The Subcommittee noted that tobramycin ampoules are listed on Section B of the Pharmaceutical Schedule with the following restriction:

Only if prescribed for dialysis or cystic fibrosis patient and the prescription is endorsed accordingly.

The Subcommittee noted in Part II of Section H of the Pharmaceutical Schedule, tobramycin ampoules are not restricted by indication, but by prescriber type, namely Infectious disease physician, clinical microbiologist or Respiratory physician. The Subcommittee noted that this situation may cause issues with access to tobramycin when patients are discharged from hospital. The Subcommittee **recommended** that access to tobramycin ampoules be widened in the community to include non-cystic fibrosis bronchiectasis.

- 1.52 The Subcommittee considered that there needed to be national leadership in antibiotic guidelines as current guidelines were not always adequate. The Subcommittee considered that taking a lead in the development of these guidelines is not PHARMACs purpose; however it considered that PHARMAC needed to be heavily involved in the development of any guidelines.

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

- 2.1 The Subcommittee noted an application for widening access to azithromycin for the prevention of exacerbations in non-cystic fibrosis related bronchiectasis.
- 2.2 The Subcommittee noted its February 2014 minute on the application for the widening access to azithromycin for non-cystic fibrosis related bronchiectasis. At that meeting, the Subcommittee requested that PHARMAC staff present a paper with minutes from the Respiratory Subcommittee of PTAC and if available, the updated Thoracic Society of Australia and New Zealand position statement to allow further review. The Subcommittee noted the tabled minutes of the Respiratory Subcommittee meeting and the requested updated position statement from the Thoracic Society of Australia and New Zealand (TSANZ).
- 2.3 The Subcommittee noted that the Respiratory Subcommittee recommended funding azithromycin for the prevention of exacerbations in non-cystic fibrosis bronchiectasis patients who had previously had at least three exacerbations in

the past 12 months with a medium priority. The Subcommittee also noted that PTAC had accepted these recommendations.

- 2.4 The Subcommittee noted that literature provided previously to the Subcommittee demonstrated that the use of azithromycin in children and adults with non-cystic fibrosis bronchiectasis has been shown to reduce the number of infective exacerbations, reduce the number of hospital admissions, increase lung function as measured by FEV1 and FVC, improve body weight, improve quality of life (QoL), increase energy, decrease in inflammatory markers, decrease the use of antibiotics for any infection in children (otitis media, skin) and cause a decrease in 24 hour sputum volume.
- 2.5 The Subcommittee noted that erythromycin is available for adult patients for exacerbations in non-cystic fibrosis related bronchiectasis. The Subcommittee considered that there is a lack of evidence to support the use of erythromycin for this indication in the paediatric population. The Subcommittee also noted the risks associated with the use of erythromycin and long QT syndrome. The Subcommittee noted that treatment of this indication in the paediatric population may result in the reversal of bronchial damage, although data is awaited to support this.
- 2.6 The Subcommittee reviewed the Thoracic Society of Australia and New Zealand Clinical Guidelines for Chronic Suppurative Lung Disease and Bronchiectasis in Children and Adults in Australia and New Zealand (2014) and an article by Chang et al entitled Management of bronchiectasis and chronic suppurative lung disease in Indigenous children and adults from rural and remote Australian communities (Med J Aust 2008;189(7): 386-393) which both support the concept that long term antibiotics should not be prescribed routinely for all cases. The Subcommittee considered that macrolides could be considered for a therapeutic trial in selected paediatric patients (for example patients with frequent exacerbations defined as 3 or more per year, or patients with 3 or more hospitalisations in the last 12 months) however it also noted that long term use of macrolides may be associated with the evolution of bacterial resistance, hearing impacts and sudden cardiac death.
- 2.7 The Subcommittee noted that azithromycin is currently listed on Section B of the Pharmaceutical Schedule as follows:

AZITHROMYCIN – Maximum of 5 days treatment per prescription; can be waived by endorsement
For Endorsement, patient has either:
1) Received a lung transplant and requires treatment or prophylaxis for bronchiolitis obliterans syndrome*; or
2) Cystic fibrosis and has chronic infection with *Pseudomonas aeruginosa* or *Pseudomonas* related gram negative organisms*.

Indications parked with * are Unapproved Indications

The Subcommittee noted the increased usage of azithromycin and expressed concern at the availability of 5 days treatment for any indication and considered that this restriction increases the risk of macrolide resistance. The Subcommittee considered that azithromycin drives macrolide resistance more than the other macrolides due to its pharmacokinetics (long half-life) and this was particularly

evident in the development of macrolide resistant *S.pneumoniae*, *S.aureus* and other nasopharyngeal pathogens. (Metzler et al - J Antimicrob Chemother 2013; 68: 631–635, Valery et al - Lancet Respir Med. 2013 Oct;1(8):610-20)

- 2.8 The Subcommittee considered that wide availability of short course azithromycin in otherwise healthy children had the potential to create significant resistance and azithromycin should not be used to treat acute pharyngitis, acute otitis media or community-acquired pneumonia. The Subcommittee also noted that support for restriction of prescribing azithromycin was seen in practice papers from both the American Academy of Pediatrics and Canadian Pediatric Society.
- 2.9 The Subcommittee considered that widening access to paediatric patients as a therapeutic trial in selected patients (for example the Thoracic Society of Australia and New Zealand recommended frequent exacerbations defined 3 or more per year, or patients with 3 or more hospitalisations in the last 12 months) for the prevention of exacerbations in non-cystic fibrosis related bronchiectasis would affect a small group of children (1 – 18 years of age) who would have increased quality of life in the short term. The Subcommittee noted that the recommended dose for azithromycin for this indication was 250mg 3 x per week (<40kg weight) or 500mg 3 x per week (≥40 kg weight). The Subcommittee considered that it was appropriate that children with non-cystic fibrosis related bronchiectasis receive azithromycin treatment for a maximum duration of 1 year with review at that point. The Subcommittee considered that after a 12 month period of treatment, reapplication with supporting evidence of improvement would be necessary to allow any further prolonged period (6-12mths) of azithromycin.
- 2.10 The Subcommittee **recommended** the application for azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis should be declined, noting that an alternative treatment is available for these patients
- 2.11 The Subcommittee **recommended** that short courses of azithromycin of 5 days treatment should be restricted to the following indications; mycoplasma genitalium infection when first line treatments have failed, pertussis and chlamydia.
- 2.12 The Subcommittee **recommended** that longer courses of azithromycin should be restricted to the following indications; patients who have received a lung transplant and require treatment or prophylaxis for bronchiolitis obliterans syndrome, patients with cystic fibrosis and have chronic infection with *Pseudomonas aeruginosa* or *Pseudomonas* related gram negative organisms, mycobacterium avium intracellulare complex infections and non-cystic fibrosis related bronchiectasis in children who have had 3 or more exacerbations of their bronchiectasis or 3 acute admissions to hospital for treatment of infective respiratory exacerbations within a 12 month period.

3 Sofosbuvir

- 3.1 The Subcommittee noted that in August 2014, PTAC reviewed an application from Gilead Sciences for the listing of sofosbuvir in the Pharmaceutical Schedule. The Subcommittee noted that PTAC recommended funding sofosbuvir for non-genotype 1 hepatitis C virus (HCV) infected patients who were on the liver transplant list with a high priority and for all other HCV patients with a low priority. The Subcommittee noted that PTAC also recommended PHARMAC seek the advice of the Anti-Infective Subcommittee and Gastroenterology Subcommittee as to any further hepatitis C infected subpopulations that were a high priority for sofosbuvir compared to currently available treatments.
- 3.2 The Subcommittee noted a paper by Gane et al. (NZMJ 2014;127(1407)). The Subcommittee noted that the number of people diagnosed with HCV in New Zealand in 2013 was 20,000; however it also noted that the total number of viraemic cases of hepatitis C in New Zealand in the same year was estimated to be 50,000. The Subcommittee noted that an estimated 1,000 new infections occurred in New Zealand in 2013. The Subcommittee noted that 99% of the diagnosed HCV infections in New Zealand are either genotype 1 (approximately 55%), 2 (approximately 5%) or 3 (approximately 40%).
- 3.3 The Subcommittee noted comments that of the 900 patients treated for HCV in New Zealand in 2013, approximately 50% of these patients are doing so as part of clinical trials.
- 3.4 The Subcommittee noted updated results from the Hepatitis Foundation's Hepatitis C Pilot (Hepatitis Foundation, Hepatitis C Programme 2015-2018 |National Implementation Plan, 19 November 2014). The Subcommittee noted that indigenous Māori are over-represented in hepatitis C at an estimated 18% of infections. The Subcommittee also noted that 16% of the patients newly diagnosed with HCV in this pilot presented with cirrhosis.
- 3.5 The Subcommittee noted a model of hepatitis C progression (Gane et al. NZMJ 2014;127(1407)). The model noted that in 2013, 25 New Zealand patients with HCV were assessed for liver transplant, and of these 12 patients received liver transplants. It further noted that between 1998 and 2013, 137 patients in total with HCV had received liver transplants, of this number 102 patients were alive, and 12 of this number are alive, post-transplant with cirrhosis and are HCV RNA positive.
- 3.6 The Subcommittee noted that the rate of progression of hepatitis C in those patients who had not be cured is accelerated post-transplant and that 25% of post-transplant patients had cirrhosis 5 years post-transplant and 15% had a liver-related mortality at 10 years post-transplant. The Subcommittee noted other HCV treatment options may be inappropriate in this subpopulation due to drug interactions as a result of immunosuppression regimens. The Subcommittee noted that almost 30% of post liver transplant patients had been cured through direct acting antiviral agent clinical trials. The Subcommittee noted that, should curative therapy be offered pre-transplant, hepatitis C treatment will not be required post-transplant and in that circumstance, it would be a finite population. The Subcommittee considered that the "pre-liver transplant with HCV" subpopulation would be an estimated 12 patients per annum ongoing and the post liver transplant with HCV subpopulation would be an estimated 12 patients

per annum ongoing, with an initial population of approximately 105 patients. The Subcommittee considered that access to sofosbuvir in the pre-liver transplant with HCV subpopulation would prevent recurrence of active HCV infection. The Subcommittee considered that access to sofosbuvir in the post-liver transplant with HCV subpopulation would prevent the requirement for re-transplant and death.

- 3.7 The Subcommittee considered that patients with HCV and decompensated cirrhosis were the patient group that has the highest priority for access to funded sofosbuvir treatment. The Subcommittee considered that the size of this patient group would be approximately 200 patients per annum. The Subcommittee considered that access to sofosbuvir treatment in this subpopulation may prevent liver transplant and death. The Subcommittee noted that treatment options for patients with cirrhosis are reduced due to issues relating to the use of peg-interferon, specifically drug interactions, anaemia and portal hypertension. The Subcommittee noted that that this in turn inhibits the use of boceprevir.
- 3.8 The Subcommittee noted the subpopulation of patients with HCV and extrahepatic manifestations. The Subcommittee considered that this subpopulation would be an estimated 10-20 patients per annum. The Subcommittee noted the extrahepatic manifestations associated with chronic HCV include essential mixed cryoglobulinaemia (with associated purpuric skin rash, cryoglobulinaemic glomerulonephritis and systemic vasculitis),
- 3.9 The Subcommittee noted that currently in New Zealand there are approximately 75 patients co-infected with human immunodeficiency virus (HIV) and HCV, with approximately 10 patients per annum being diagnosed with HCV and HIV. The Subcommittee noted that the effect of co-infection is to increase the rate of disease progression; however it was noted that a patient who was co-infected with HCV and HIV would progress through the same disease stages as a patient who was not co-infected with HCV and HIV. The Subcommittee considered that being co-infected with HCV and HIV is not, in itself, a reason to prioritise funding with sofosbuvir.
- 3.10 The Subcommittee noted that another subpopulation that could be identified was patients with HCV and cirrhosis. The Subcommittee considered that this subpopulation is currently approximately 3500 patients in New Zealand, with an additional 300 patients per annum being diagnosed with HCV and cirrhosis. The Subcommittee considered that treatment with sofosbuvir in this group may reverse fibrosis, but treatment would not reduce the increased risk of hepatocellular carcinoma experienced by this subpopulation, and members considered patients diagnosed with a hepatocellular carcinoma would have a one-year life expectancy. The Subcommittee noted that treatment options for patients with cirrhosis are reduced due to issues relating to the use of peg-interferon, specifically drug interactions, anaemia and portal hypertension. The Subcommittee noted that that this in turn inhibits the use of boceprevir.
- 3.11 The Subcommittee noted information relating to Auckland District Health Board's experience with boceprevir in treating patients with HCV over the past year. ADHB had treated 17 patients, of whom 11 were treatment-naive, non-CC, cirrhotic and six were responder-relapsers to peg-interferon in combination with

- ribavirin. The Subcommittee noted that 11 of these patients completed treatment; 3 patients achieved a sustained viral response, 4 patients relapsed and 4 had no response.
- 3.12 The Subcommittee noted results from a number of phase 3 programmes relating to the use of sofosbuvir in combination with ribavirin (Zeuzem S, et al. *N Engl J Med* 2014; online 4 May DOI: 10.1056, Lawitz E, et al. *N Engl J Med* 2013; 368:1878-87, Jacobson IM, et al. *N Engl J Med* 2013;368:1867-77). The Subcommittee noted that as a result of this data the FDA had recommended, for patients with HCV genotype 2, 12 weeks of sofosbuvir in combination with ribavirin, and that this gives a Sustained Virological Response at 12 weeks post-treatment (SVR-12), of 98%. The Subcommittee noted that for patients with HCV genotype 3, 24 weeks of sofosbuvir and ribavirin therapy are demonstrated to give an SVR-12 of 94%. The Subcommittee noted that the FDA recommends 12 weeks of sofosbuvir treatment in combination with peg-interferon and ribavirin for patients HCV genotype 1(SVR-12 90%) or HCV genotype 4 (SVR-12 96%). The Subcommittee noted that the American Association for the Study of Liver Disease (AASLD) and the Infectious Diseases Society of America (IDSA) recommends 12 weeks of sofosbuvir therapy in combination with peg-interferon and ribavirin, and this gives a SVR-12 of 83%. The Subcommittee noted that in this same group, SVR-12 of 87% in non-cirrhotic patients and 60% in cirrhotic patients could be achieved with 24 weeks of sofosbuvir in combination with ribavirin.
- 3.13 The Subcommittee noted that a single tablet regimen of ledipasvir with sofosbuvir (Harvoni) has been granted Medsafe approval in November 2014. The Subcommittee noted that a number of other all oral direct acting antiviral hepatitis C treatments which result in interferon free regimens are in development. The Subcommittee noted that initial information relating to treatments are promising with benefits such as reduced treatment time and pan-genotypic qualities being demonstrated.
- 3.14 The Subcommittee considered that a delay in access to effective HCV treatment would result in a longer delay until the peak of HCV cases occurred and would have a negative impact on longer-term morbidity and mortality and cost to the health sector.
- 3.15 The Subcommittee noted the PTAC recommendation to only fund sofosbuvir with a high priority for HCV non-genotype 1 patients who are awaiting liver transplant. Members noted that this was inappropriate as boceprevir could not be used in decompensated patient and therefore there was no clinical difference between a genotype 1 patient and all other hepatitis C patients on the transplant list in terms of treatment options. The Subcommittee further noted that interferon containing regimens (such as boceprevir with interferon and ribavirin) are contraindicated in in patients with advanced cirrhosis (CUPIC Study Group - Hezode et al. *Gastroenterology* 2014;147:132–142). The Subcommittee considered that interferon containing regimens would therefore be contraindicated in patients on the transplant list with decompensated cirrhosis or HCV related hepatocellular carcinoma.

- 3.16 The Subcommittee noted that other patient groups, including patients with compensated cirrhosis, could be considered should price reductions occur. The Subcommittee would provide advice relating to these groups should this be an option.
- 3.17 The Subcommittee **recommended** that sofosbuvir should be funded with a high priority for the following subpopulations:
- HCV patients with decompensated cirrhosis (all genotypes)
 - HCV patients pre/post liver transplant (all genotypes)
 - HCV patients, genotype 1, 2 and 3, with essential mixed cryoglobulinaemia (with associated purpuric skin rash, cryoglobulinaemic glomerulonephritis and systemic vasculitis),
- 3.18 The Subcommittee **recommended** that sofosbuvir should be funded for all other subpopulations with a low priority.

4 Micafungin

- 4.1 The Subcommittee noted that at its meeting on 7 November 2014, PTAC discussed a supplier application for micafungin powder for injection for the treatment of invasive candidiasis, for the treatment of oesophageal candidiasis in patients aged 16 and over for whom intravenous therapy is inappropriate, and for prophylaxis of *Candida* infection in children and adult patients undergoing allergenic haematopoietic stem cell transplantation or patients who are expected to have neutropenia. The Subcommittee noted that PTAC had deferred making a recommendation on the funding of Mycamine (micafungin powder for injection) pending review of the application by the Anti-Infective Subcommittee of PTAC. The Subcommittee noted that PTAC requested specific advice relating to:
- (a) Whether there are any advantages of micafungin over the currently available funded treatments;
 - (b) How micafungin would be used in practice;
 - (c) The anticipated dose of micafungin.
- 4.2 The Subcommittee noted that micafungin is an echinocandin, a class of antifungal drugs that are semisynthetic lipoproteins produced via chemical modifications of natural products of fungi. The Subcommittee also noted that caspofungin is also an echinocandin and is a currently listed treatment for candidemia in DHB hospitals restricted to proven or probable invasive fungal infection on the recommendation of certain specialties.
- 4.3 The Subcommittee considered that micafungin is non-inferior to caspofungin for treatment of candidiasis. Members noted that caspofungin was indicated for the treatment of invasive aspergillus while micafungin was not which may limit its usage in DHB hospitals.

- 4.4 The Subcommittee noted that the recommended dosing for caspofungin was 70mg loading dose, then 50mg daily. Members considered that the anticipated dose of micafungin would be 150mg daily or 100mg daily for patients with oesophageal candidiasis or invasive candidiasis.
- 4.5 The Subcommittee considered that there is no unmet clinical need in the patient populations identified in the application.
- 4.6 The Subcommittee **recommended** micafungin be funded for the treatment of invasive candidiasis, for the treatment of oesophageal candidiasis in patients aged 16 and over for whom intravenous therapy is inappropriate, and for prophylaxis of *Candida* infection in children and adult patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia, if cost neutral to caspofungin over the life of the patent.

5 Dolutegravir

- 5.1 The Subcommittee considered an application from GlaxoSmithKline to fund Tivicay (dolutegravir sodium) for the treatment of HIV infection in treatment naïve and treatment experienced patients (adults and children over 12 years of age and weighing 40 kg or more).
- 5.2 The Subcommittee noted that Tivicay (dolutegravir sodium) is an integrase strand transfer inhibitor (INSTI) that blocks the strand transfer reaction required for the integration of viral cDNA into the host's genome. Members noted that Tivicay is administered as one tablet once daily for the treatment of HIV infection in combination with other antiretroviral agents in adults and children over 12 years of age and weighing 40kg or more.
- 5.3 The Subcommittee considered that the strength and the quality of the evidence supplied in the application was high. The Subcommittee considered that the pivotal evidence to support the efficacy of dolutegravir comes from two double-blind randomised, phase III studies:
- (a) Raffi et al (Lancet Infect Dis. 2013;13(11):927-35). A phase 3, non-inferiority study of treatment naïve patients with an HIV-1 RNA concentration of 1000 copies per mL or more. Patients were randomly assigned (1:1) to receive either dolutegravir (Tivicay) or raltegravir and matching placebo in combination with investigator-selected NRTI backbone (tenofovir-emtricitabine or abacavir-lamivudine). The primary endpoint was HIV RNA concentration of 50 copies per mL or less after 48 weeks, with a 95% confidence interval of -1.1 to 10% confirming non-inferiority. 1035 patients were screened, 827 were randomly assigned to study group, and 822 were treated (411 with dolutegravir, 411 with raltegravir).

The Subcommittee noted dolutegravir was non-inferior to raltegravir for the primary outcome (332 patients [81%] vs 314 [76%], adjusted difference 4.5 %, 95% CI -1.1 to 10). Pre-specified secondary objectives of virological outcomes from baseline viral load or NRTI backbone were

supportive of non-inferiority (CD4 cell count median increase 276 cells per mL vs 264 cells per mL). Tolerability and safety was favourable across both regimens, 10 patients (2%) in each group discontinued treatment due to adverse events. Small mean increases in serum creatinine concentration occurred in both study groups by week 2 and remained stable through week 96 (mean change 14.6 µmol/L vs 8.2 µmol/L). Grade 1 treatment emergent creatinine toxic effects were noted in 14 vs 8 patients.

- (b) Cahn et al (Lancet. 2013;382(9893):700-8) - a phase 3, non-inferiority study of antiretroviral-experienced, integrase-inhibitor-naïve adults randomly assigned (1:1) to receive dolutegravir (Tivicay) or raltegravir with investigator-selected background therapy plus matching placebo. Eligibility criteria included two consecutive plasma HIV1 RNA assessments with concentration of 400 copies per mL or higher (unless >1000 copies per mL at screening), resistance to two or more classes of antiretroviral drugs, and had one to two fully active drugs for background therapy (at least one fully active agent with or without a second agent, with or without full activity). The primary endpoint was HIV RNA concentration of fewer than 50 copies per mL at week 48, with a 12% non-inferiority margin. 715 patients were randomly assigned and treated (354 with dolutegravir, 361 with raltegravir). Dolutegravir was non-inferior to raltegravir; 251/354 (71%) vs 230/361 (64%) of patients had HIV concentrations of fewer than 50 copies per mL at week 48 (adjusted difference 7.4%, 95% CI 0.7 to 14.2). The main pre-specified and α -controlled secondary endpoint of treatment-emergent genotypic or phenotypic integrase inhibitor resistance was lower for dolutegravir (4/354 (1%) x 17/361 (5%).
- 5.4 The Subcommittee considered that dolutegravir has a similar clinical effect to raltegravir; however members considered that dolutegravir was a more virologically active agent. Dolutegravir is not licensed for children aged under 12 years whereas raltegravir is licensed from infancy. Members considered that dolutegravir's once daily formulation may provide some advantage over other therapies in terms of enhanced compliance. The Subcommittee noted that there is the possibility of a drug-drug interaction between dolutegravir and metformin.
- 5.5 The Subcommittee considered that currently, there is no unmet need in this patient population.
- 5.6 The Subcommittee **recommended** the listing of dolutegravir on Section B and Part II of Section H Schedule for the treatment of HIV infection, under the current Special Authority and restriction to antiretroviral therapy for HIV treatment, only if cost-neutral for the life of the raltegravir patent.