

Anti-Infective Subcommittee of PTAC
Meeting held 4 November 2015

(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 contains 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 11 & 12 February 2016.

Record of the Anti-Infective Subcommittee of the Pharmacology and Therapeutics Committee (PTAC) meeting held at PHARMAC on 4 November 2015

1 Correspondence

Moxifloxacin for penicillin allergic patients post-splenectomy

- 1.1 The Subcommittee noted correspondence from the Antimicrobial Stewardship Committee requesting consideration for access to moxifloxacin as a “standby” antibiotic for asplenic individuals who have immediate hypersensitivity reactions to penicillins.
- 1.2 The Subcommittee noted that the group of asplenic patients with a true allergy to penicillin would be very small, with approximately 20 patients nationally, and that some of these patients would still be able to use alternatives such as cephalosporins. Members considered that, should moxifloxacin be available for patients post-splenectomy, then the names of those accessing this treatment would coincide with those listed on a splenectomy register should one be available .
- 1.3 The Subcommittee noted that ESR produce reports which document invasive pneumococcal disease cases in NZ. It noted that these reports include information about which cases are reported as having anatomical or functional asplenia. The Subcommittee noted that the denominator detailing number of splenectomised patients is unknown and considered that this indicates the need for a registry. This would enable ESR to produce reports which estimated rates of invasive pneumococcal disease in this high risk group.
- 1.4 The Subcommittee noted that national access to immunologists for the testing of penicillin allergy was not consistent. However, the members also considered that it would be very worthwhile for any patient in this position to confirm whether or not they had a true penicillin allergy.
- 1.5 The Subcommittee considered that it would be appropriate for moxifloxacin to be dispensed to patients in this situation under the supervision of a hospital infectious diseases physician or clinical microbiologist. The Subcommittee did not consider that moxifloxacin should be dispensed in the community for this indication. The Subcommittee noted that there is no dosage information for moxifloxacin use in children and that currently oral moxifloxacin is only available as a single tablet size of 400mg. The Subcommittee noted that this may not be suitable for children. One member noted that would not be an acceptable alternative for children who have higher rates of carriage of resistance pneumococci and also high rates of invasive pneumococcal disease.
- 1.6 The Subcommittee recommended add the following restriction to moxifloxacin on Part II of Section H of the Pharmaceutical Schedule as below with a medium priority.

Restricted

Post -splenectomy patient with confirmed allergy to penicillin

Infectious disease specialist or clinical microbiologist

All of the following:

1. Patient has had a splenectomy; and
2. Patient has or Stevens-Johnson syndrome/TEN or confirmed immediate hypersensitivity reaction to penicillin as determined by an immunologist.

Moxifloxacin for patients with moderate to severe pneumonia who have a history of severe penicillin or cephalosporin allergy

- 1.7 The Subcommittee noted correspondence from an infectious diseases physician requesting consideration for access to moxifloxacin on the Hospital Medicines List (HML) for the treatment of moderate to severe pneumonia in patients who have a history of severe penicillin or cephalosporin allergy.
- 1.8 The Subcommittee noted that many allergies to medications were unproven and histories of adverse reactions were often anecdotal only. The Subcommittee considered that its recommendations play an important role in antibiotic stewardship.
- 1.9 The Subcommittee considered that there are a number of other effective options already available for this small set of patients which would include macrolide therapy. The Subcommittee recommended that the requested change to the HML be declined.

Cefuroxime liquid for paediatric use

- 1.10 The Subcommittee reviewed correspondence relating to recent clinical practice guidelines for acute otitis media (AOM), including the South Australian Paediatric Practice Guidelines for Acute Otitis Media in Children (<https://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/resources/policies/acute+otitis+media+in+children+-+sa+paediatric+clinical+guideline>) and the American Academy of Pediatrics guidelines for the Diagnosis and Management of Acute Otitis Media (<http://pediatrics.aappublications.org/content/131/3/e964.full-text.pdf>). The Subcommittee noted that the guidelines presented indicated a role for cefuroxime for paediatric patients who are allergic, intolerant, or resistant to penicillins.
- 1.11 The Subcommittee noted that there was no cefuroxime oral liquid currently registered in New Zealand.
- 1.12 The Subcommittee considered that cefalexin is available in a palatable paediatric form which provides coverage for some organisms. However it was also noted there is no clinical outcome data for the use of cephalexin in AOM. The Subcommittee also considered that the number needed to treat is high.
- 1.13 The Subcommittee noted cefaclor (a second generation cephalosporin) is also available and could be used for patients with penicillin allergy. However, the

Subcommittee noted there are some concerns about efficacy and side effects with cefaclor which may make it a second choice after cefuroxime.

- 1.14 The Subcommittee considered patients with failure to first line amoxicillin (rather than suspected allergy), second line options would include amoxicillin + clavulanic acid syrup particularly if a reduced clavulanic acid dosing preparation was available in NZ which would lessen the diarrhoeal side effect.
- 1.15 Members considered that macrolides would be used where a patient had severe penicillin allergy.

Antiretroviral therapy for people with HIV infection – reconsideration of the Subcommittee's recommendation

- 1.16 The Subcommittee noted the correspondence that PHARMAC had received from the New Zealand AIDS Foundation requesting that the proposal to amend the access criteria to antiretrovirals be reconsidered in light of the recent data.
- 1.17 The Subcommittee noted its previous discussion and recommendation that the Special Authority for access to antiretrovirals be amended to allow access to antiretrovirals to all people diagnosed with HIV. It noted that it had given a medium priority to this recommendation in February 2014.
- 1.18 The Subcommittee noted the report by the INSIGHT START study group on the Strategic Timing of Antiretroviral Treatment (START) trial (The INSIGHT START Study Group, N Eng J Med: 2015;373:795-807). The Subcommittee noted that the START trial ended sooner than predicted as a result of the study question relating to the benefits and risks of early initiation of antiretroviral having been answered. The Subcommittee noted that the World Health Organization (WHO) has changed its recommendation in the interest of both individual and public health gains, to any HIV positive patient who was ready to commence therapy should do so.
- 1.19 Members reiterated their estimate that, should access be widened to allow access to all people diagnosed with HIV to antiretrovirals, that this would result in a less than 5% increase in new patients who would be initiated on therapy over status quo. Members understood that there were approximately 1000 HIV positive patients in the Auckland region, of whom ~91% were currently on treatment. Of those patients who were not on treatment, approximately half (~4.5%) did not meet the Special Authority criteria for access. The remaining half had chosen not to commence treatment for a variety of reasons.
- 1.20 Members noted that the current Special Authority criteria allow access to antiretrovirals to people with HIV who are considered to be symptomatic, regardless of their CD4 count. The Subcommittee noted that the term 'symptomatic' in the Special Authority had not been defined, and considered prescribers could/would apply this to a variety of symptoms (beyond those symptoms and/or sequelae classically associated with opportunistic infections).
- 1.21 The Subcommittee noted notification and other-sourced surveillance data compiled by the AIDS Epidemiology Group (University of Otago) provided for the

Ministry of Health (MoH) regarding the prevalence of HIV positive adults in New Zealand. Members considered that this was likely to overestimate true numbers. Members noted impending information in relation to the assumptions made to produce the data. Members noted that the data do not reflect the number of patients who leave the country. In addition, members considered HIV positive patients who died of unrelated causes were unlikely to have their HIV status reported on their death certificate which likely causes delays in reporting the subsequent change in the number of HIV positive people in New Zealand.

- 1.22 The Subcommittee considered that in New Zealand, early treatment of people with HIV would mostly be of public health benefit through reduced rates of interpersonal transmission rather than improving the health of individual patients with established infection. Members noted that the most benefit in terms of reduced transmission would be gained from targeting patients early in their diagnosis as people are most infectious within the first 6 months of contracting the virus. Members considered that a test-and-treat approach would be most beneficial in terms of reducing transmission. Members noted that modelling on individual patient health gains based on the START study would provide a larger number needed to treat to avoid a significant event, which would likely give a relatively poor cost benefit outcome. The Subcommittee considered that the current requirement that initiation of antiretroviral treatment be made by a registered antiretroviral prescriber remains appropriate and should not change.
- 1.23 Members provided a paper on the potential impact on HIV transmission through earlier antiretroviral initiation in (Phillips et al. AIDS. 2015;29:1855-62). The paper describes a dynamic individual-based simulation model that estimates future HIV transmission in the UK in men who have sex with men (MSM), based on changes to testing and ART treatment scenarios. The Subcommittee considered this paper could be used by PHARMAC staff to inform assumptions on transmission reduction in its economic modelling.
- 1.24 The Subcommittee reiterated its recommendation that the following changes be made to the Special Authority (additions marked in bold and deletions in strikethrough) with a medium priority:

Initial application - (Confirmed HIV/AIDS) only from a named specialist. Approvals valid without further renewal unless notified for applications meeting the following criteria:

Beth:

1. **where the patient has** confirmed HIV infection. **and**
- 2. Any of the following:**
 - 2.1 Symptomatic patient;** or
 - 2.2 Patient aged 12 months and under;** or
 - 2.3 Beth:**
 - 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/mm³**
 - 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 Beth:**
 - 2.4.1 Patient aged 6 years and over;** and
 - 2.4.2 CD4 counts < 500 cells/mm³**

2 Matters Arising

Antibacterials

Amoxicillin with clavulanic acid granules for oral liquid

- 2.1 The Subcommittee noted that PHARMAC staff had been approached by the supplier of a 400mg/5mL amoxicillin and 57mg/5mL clavulanic acid formulation and were requesting clinical advice on the product.
- 2.2 The Subcommittee considered that this formulation with its reduction in clavulanic acid was an advantage as it would result in less side-effects without a loss in efficacy. The Subcommittee noted that this formulation is available in Australia.
- 2.3 The Subcommittee considered that, should this product be subsidised, an education campaign aimed at general practitioners, nurses, and pharmacists would be required to ensure appropriate prescribing, particularly in the form of standing orders. The Subcommittee considered that appropriate forms of a campaign may include information via letter. The Subcommittee recommended that, should this change happen, PHARMAC staff inform the New Zealand Formulary, as it noted that any change may result in information on the formulary's website becoming incorrect.
- 2.4 Of the three new products, the Subcommittee indicated a preference for the 400/57 strength, but noted that all formulations would likely be tendered.
- 2.5 The Subcommittee tasted both the current product and the new products and considered both brands to be palatable.

Treatments for rosacea – update

- 2.6 The Subcommittee noted the relevant minutes from its previous meeting on minocycline hydrochloride for the treatment of rosacea. The Members also noted that this product was to be reviewed at the next Dermatology Subcommittee meeting on 30 November 2015.
- 2.7 The Subcommittee noted the minutes from the Tender Medical Evaluation Subcommittee on 19 & 20 February 2015, where the TMESC recommended consideration of lymecycline for rosacea.
- 2.8 The Subcommittee noted that there is limited evidence in terms of data available to support the use of lymecycline in this indication.

Flucloxacillin

- 2.9 The Subcommittee noted the current Practitioner Supply Order (PSO) situation as it relates to flucloxacillin capsules. The Subcommittee recommended that a PSO is added to the 500 mg capsule.

Antifungals

Posaconazole modified release tablets

- 2.10 The Subcommittee noted that PHARMAC has received a commercial proposal from a supplier for posaconazole modified release tablets.
- 2.11 The Subcommittee noted that there are a number of issues related to the use of posaconazole liquid including palatability and the requirement that it is taken with a high-fat meal. The Members considered that a number of these issues could be overcome with the introduction of a modified release tablet. However the Subcommittee emphasised that a liquid formulation should remain available for paediatric use.

Antitrichomonal agents

Metronidazole – request to consider PSO for 400 mg tablets

- 2.12 The Subcommittee noted that PHARMAC had received correspondence requesting consideration of the addition of a Practitioners Supply Order (PSO) to metronidazole 400 mg tablets.
- 2.13 The Subcommittee noted that there was a current PSO on Section B of the Pharmaceutical Schedule for up to 30 metronidazole 200 mg tablets. However, members also noted that for patients diagnosed with metronidazole sensitive STIs, the recommended stat dose of 2 g to treat the infection would require 10 x 200 mg tablets, which members considered impractical.
- 2.14 The Subcommittee recommended adding a PSO to metronidazole 400 mg tablets and the removal of the PSO from the 200 mg metronidazole tablets.

Urinary Tract Infections (UTIs)

Nitrofurantoin

- 2.15 The Subcommittee noted that PHARMAC staff had been notified by a supplier of its ability to supply nitrofurantoin modified release capsules to New Zealand.
- 2.16 The Subcommittee noted the following data provided to support the use of the modified release formulation:
- The Society of Obstetricians and Gynaecologists of Canada, Clinical Practice Guidelines on recurrent UTI, 2010 (<http://sogc.org/guidelines/recurrent-urinary-tract-infection/>)
 - Crystalline and macrocrystalline nitrofurantoin in the treatment of UTI (Kalowski, NEJM, 1974, 290: 385-87)
 - Long term nitrofurantoin treatment of post-operative secondary pyelonephritis (Makrigiannis & Gaca, International Urology and Nephrology, 1970, 2:353-358)

- 2.17 The Subcommittee noted that modified release nitrofurantoin requires twice daily dosing, compared with immediate release nitrofurantoin which requires four times daily dosing. The Subcommittee considered the current dosing requirement for nitrofurantoin may discourage practitioners from prescribing and/or patients receiving this pharmaceutical and that, as an alternative, other antibiotics, such as norfloxacin and amoxicillin with clavulanic acid, may be used. Members therefore considered that nitrofurantoin modified release may provide some benefit in terms of antibiotic stewardship. The Subcommittee noted that nitrofurantoin is only indicated for urinary tract infections.
- 2.18 The Subcommittee noted that nitrofurantoin modified release is associated with adverse events such as pulmonary fibrosis and hepatic dysfunction. The Subcommittee considered that, should nitrofurantoin modified release be subsidised, prescriber education would be advisable to highlight these potential issues.
- 2.19 The Subcommittee recommended that nitrofurantoin modified release capsules be funded with high priority.

3 Update from PTAC discussions on tobramycin and azithromycin for non-cystic fibrosis bronchiectasis

- 3.1 The Subcommittee noted a paper by PHARMAC staff that detailed the previous discussion made by PTAC and its Subcommittees, including the Anti-infective Subcommittee and the Respiratory Subcommittee regarding proposals for azithromycin and tobramycin for non-cystic fibrosis (non-CF) bronchiectasis.
- 3.2 The Subcommittee noted that at its meeting in August 2015, PTAC recommended that the application for use of tobramycin for the use of non-CF bronchiectasis be declined and that the application for azithromycin for prevention of exacerbations in adult non-CF bronchiectasis also be declined.
- 3.3 The Subcommittee noted that PTAC recommended that azithromycin be funded for non-CF bronchiectasis in children (aged 18 or under) 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, for a maximum duration of 24 months of therapy, with a high priority. The Subcommittee noted that this recommendation aligned with the previous recommendations the Anti-infective Subcommittee had made in relation to this treatment.

4 Valganciclovir

Recommendation

- 4.1 The Subcommittee considered that it could not support a widening of access for valganciclovir for lung transplant recipients who require prophylaxis to prevent CMV reactivation during steroid pulse therapy and **recommended** that the application be declined.

Discussion

- 4.2 The Subcommittee noted correspondence from a Respiratory Physician, in relation to the Special Authority (SA) criteria for valganciclovir. The correspondent requested consideration for the SA to be extended to include lung transplant recipients who require prophylaxis to prevent cytomegalovirus (CMV) reactivation during steroid pulse therapy.
- 4.3 The Subcommittee noted that valganciclovir was reviewed by the Transplant Immunosuppressant Subcommittee at its meeting on 11 May 2015. The Transplant Immunosuppressant Subcommittee recommended that the SA for valganciclovir be amended to include renewal criteria for patients who had undergone a lung transplant and received pulse methylprednisolone for acute rejection after the initial 6 months of CMV prophylaxis and require a further 90 days of valganciclovir for CMV prophylaxis. The Transplant Immunosuppressant Subcommittee had also recommended that the Anti-Infective Subcommittee be asked for advice on widening access of valganciclovir to other organ transplant recipients with augmented immunosuppression, at risk of CMV and/or Epstein - Barr virus (EBV).
- 4.4 The Subcommittee considered that, although some guidelines support consideration of valganciclovir in lung transplant recipients who require prophylaxis to prevent CMV reactivation during steroid pulse therapy, there is no data to support valganciclovir prophylaxis in this setting. The Subcommittee considered that there is variation in practice in this situation.
- 4.5 The Subcommittee considered that there is no data to support the use of valganciclovir for the treatment or prophylaxis of EBV reactivation. The Subcommittee further considered that there is no data to support the use of valganciclovir for the treatment or prophylaxis of post-transplant lymphoproliferative disorder.

5 Lamivudine

Recommendation

- 5.1 The Subcommittee **recommended** that lamivudine be funded for hepatitis B (HBV) reactivation prophylaxis for immunocompromised patients with a high priority. The Subcommittee recommended that "immunocompromised" be defined

as “any malignancy receiving rituximab and other immunosuppressant chemotherapies”.

Discussion

- 5.2 The Subcommittee noted that in December 2014, PHARMAC received correspondence in relation to lamivudine for the prevention of HBV reactivation in hepatitis B surface antigen (HBsAg) negative/ hepatitis B core antibody (anti-HBc) positive patients who are receiving treatment with rituximab in combination with other immunosuppressant medication.
- 5.3 The Subcommittee noted the costs associated with the recommended monitoring of HBV DNA and questioned whether prophylactic treatment with lamivudine would be a more cost effective option when compared with HBV DNA monitoring.
- 5.4 Members noted that it last considered access to lamivudine in relation to prophylaxis for immunosuppressed patients in February 2014.
- 5.5 The Subcommittee noted the report by Kusumoto and Tobinai (Screening for and management of hepatitis B reactivation in patients treated with anti B cell therapy – Hematology 2014;2014:576-583). It noted that the authors considered that it is reasonable for patients HBsAg (-)/ anti-HBc (+) or HBsAg (-)/ anti-HBs (+) who have undetectable HBV DNA levels to undergo regular HBV DNA monitoring-guided pre-emptive antiviral therapy. The paper considered that patients HBsAg (-)/ anti-HBc (+) or HBsAg (-)/ anti-HBs (+) with detectable HBV DNA levels should receive anti-viral prophylaxis.
- 5.6 The Subcommittee noted the British Columbia Cancer Agency (BCCA) 2014 Protocol summary for treatment of chronic lymphocytic leukemia (CLL) or prolymphocytic leukemia with fludarabine, cyclophosphamide and rituximab ([http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Lymphoma-Myeloma/LYFCR Protocol 1Jul2014.pdf](http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Lymphoma-Myeloma/LYFCR%20Protocol%201Jul2014.pdf), availabile from <http://www.bccancer.bc.ca/>). The Members noted the London Cancer Group Hepatitis B infection in Patients Undergoing Chemotherapy-Prevention and management guidelines 2014 (<http://www.londoncancer.org/media/80152/London-Cancer-Guideline-Hepatitis-guidelines-v1.1.pdf>) and the two possible approaches detailed in these guidelines, one involving the monitoring of HBV levels and the other using lamivudine pre-emptive therapy.
- 5.7 The Subcommittee noted the Cancer Institute of New South Wales 2014 guidelines, Hepatitis B Screening and Prophylaxis in Cancer Patients Requiring Cytotoxic and/or Immunosuppressive Therapy (<https://www.eviq.org.au/Protocol/tabid/66/id/1382/Default.aspx> on 09/10/2015). Members also noted the Seto et al paper, Hepatitis B Reactivation in Patients With Previous Hepatitis B Virus Exposure Undergoing Rituximab-Containing Chemotherapy for Lymphoma: A Prospective Study (J Clin Oncol. 2014;32:3736-43).
- 5.8 The Subcommittee noted a paper by Koo et al, Risk of hepatitis B virus (HBV) reactivation in hepatitis B surface antigen negative/hepatitis B core antibody

positive patients receiving rituximab-containing combination chemotherapy without routine antiviral prophylaxis (Ann Hematol. 2011;90:1219-23). The Subcommittee noted that hepatitis B reactivated in two patients, both of whom were receiving rituximab in patients who were also receiving corticosteroids.

- 5.9 The Subcommittee noted the European Association for the Study of the Liver (EASL) clinical practice guidelines (The EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection. J Hepatol. 2012;57:167-85) and its recommendation that HBsAg-negative, anti-HBc positive patients with detectable serum HBV DNA should be treated similarly to HBsAg positive patients. It noted the American Association for the Study of Liver Diseases (AASLD) guidelines (Chronic Hepatitis B: Update 2009 Hepatology. 2009;50:661-2) and the Australia and New Zealand Chronic Hepatitis B Recommendations (Digestive Health Foundation, 2008).
- 5.10 The Subcommittee noted the results of the Hui et study, Kinetics and risk of de novo hepatitis B infection in HBsAg-negative patients undergoing cytotoxic chemotherapy (Gastroenterology. 2006;131:59-68) and its recommendation that surveillance of HBV DNA in HBsAg-negative patients treated with chemotherapy be performed so that early commencement of antiviral therapy can be initiated before the occurrence of de novo HBV-related hepatitis.
- 5.11 The Subcommittee noted that if rituximab in patients HBsAg - /HBc + was used as the criterion for initiation of lamivudine prophylaxis, then it would include all indications of rituximab including rheumatoid arthritis. The Subcommittee noted the results of the Barone et al study (Safety of long-term biologic therapy in rheumatologic patients with a previously resolved hepatitis B viral infection, Hepatology 2015;62:40-46). The Subcommittee considered that lamivudine prophylaxis should be restricted to patients with malignancy receiving rituximab in combination with immunosuppressant chemotherapies.
- 5.12 The Subcommittee considered that the number of patients with this indication would be small.