Anti-Infective Subcommittee of PTAC
Meeting held 13 October 2016

(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 9 & 10 February 2017.

Record of the Anti-Infective Subcommittee of the Pharmacology and Therapeutics Committee (PTAC) meeting held at PHARMAC on 13 October 2016

1 Ceftolozane and tazobactam

Application

1.1 The Subcommittee reviewed a funding application from Merck, Sharp and Dohme (MSD) for the listing of combination ceftolozane with tazobactam for intravenous infusion (Zerbaxa) in Section H of the Pharmaceutical Schedule for the treatment of confirmed or suspected resistant gram negative infections.

Recommendation

1.2 The Subcommittee **recommended** that the application as proposed be declined.

1.3 The Subcommittee **recommended** that it reviews evidence on the use of ceftolozane with tazobactam for the treatment of *Pseudomonas* in cystic fibrosis patients when data becomes available.

Discussion

1.4 The Subcommittee noted that ceftolozane with tazobactam was indicated for the empiric treatment of complicated intra-abdominal infections (cIAI) in combination with metronidazole, and for complicated urinary tract infections (cUTI) including pyelonephritis.

1.5 The Subcommittee noted that ceftolozane with tazobactam combines a novel 5th generation cephalosporin with an established β-lactamase inhibitor that has broad activity against a range of gram negative bacteria.

1.6 The Subcommittee reviewed evidence from ASPECT-cUTI, a randomised, multicentre, double blind, double-dummy, non-inferiority phase 3 trial (Wagenlehner et al, Lancet 2015; 385:1949-56). Members noted that this trial randomised 1083 patients with a complicated UTI including pyelonephritis to receive a seven day course of either 1.5 g IV ceftolozane with tazobactam every 8 hours (n=543) or 750 mg IV levofloxacin once daily (n=540). Members noted that the primary endpoint of the trial was a composite of microbiological eradication and clinical cure 5–9 days after treatment in the microbiological modified intention-to-treat (MITT) population, with a non-inferiority margin of 10%. Members further noted that of the 1083 patients enrolled, 800 (73·9%), of whom 656 (82·0%) had pyelonephritis, were included in the microbiological MITT population. The Subcommittee noted that results from the ASPECT-cUTI study demonstrated that ceftolozane with tazobactam was non-inferior to levofloxacin for composite cure in the microbiological MITT and per-protocol populations.

1.7 The Subcommittee also reviewed evidence from ASPECT-cIAI, a prospective, randomised, multicentre, double-blind, phase 3 trial (Solomkin et al, Clin Infect Dis 2015; 60:1462-1471). Members noted that this trial randomised 933 hospitalised patients with clinical evidence of cIAI to receive 1.5 g IV ceftolozone

with tazobactam (n=487) every 8 hours plus 500mg metronidazole every 8 hours or 1 g IV meropenem every 8 hours plus placebo (n=506) for 4-14 days. Members noted that the trial objectives were to demonstrate statistical non-inferiority in clinical cure rates at the test-of-cure visit (24–32 days from start of therapy) in the microbiological intent-to-treat (primary) and microbiologically evaluable (secondary) populations using a non-inferiority margin of 10%. Members noted that results demonstrated that ceftolozane with tazobactam plus metronidazole was non-inferior to meropenem in the primary (83.0% [323/389] vs 87.3% [364/417]; weighted difference, −4.2%; 95% confidence interval [CI], −8.91 to .54) and secondary (94.2% [259/275] vs 94.7% [304/321]; weighted difference, −1.0%; 95% CI, −4.52 to 2.59) endpoints. Members noted lower cure rates in patients with moderate renal failure (creatinine clearance 30-50 mL/min) and those aged 65 or older. Referenced also archived drug label available at www.dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=183814

1.8 The Subcommittee considered that ceftolozane with tazobactam appeared to be well tolerated. However, members noted a precaution on the datasheet for use in elderly patients and those with renal impairment. Members noted that the data sheet recommended that because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function and adjust dosage based on renal function. Members considered that this potentially limited its usefulness in older patients which constituted a substantial proportion of the cUTI and cIAI populations. Members further noted that ceftolozane with tazobactam was administered by IV infusion every 8 hours, which was not as convenient as once daily dosing with the alternative funded treatment option of IV gentamicin or ceftriaxone plus trimethoprim or ciprofloxacin (twice daily) in cUTIs.

1.9 Overall, whilst the Subcommittee acknowledged that ceftolozane with tazobactam was efficacious, it considered that it did not provide meaningful benefits as an empiric treatment over the currently funded treatments options and was substantially more expensive. Members further considered that for cUTI patients, ceftolozane with tazobactam dosing was less convenient than the currently funded treatment options. Members considered that ceftolozane with tazobactam may be a useful treatment option for patients with multidrug resistance infections where current treatment options would not be suitable, members considered that these should situations be considered on a case by case basis via the NPPA process.

1.10 The Subcommittee noted an ongoing trial of ceftolozane with tazobactam in cystic fibrosis patients with *Pseudomonas aerugeinosa* infection. Members considered this may be a useful treatment for this patient groups and requested that the supplier provide the data for this indication when it was available.

2 Azithromycin update

2.1 The Subcommittee noted that, in May 2015, the Pharmacology and Therapeutics Advisory Committee (PTAC) reviewed the minutes from this Subcommittee's December 2014 meeting and accepted the Subcommittee's recommendations regarding indication restrictions on the use of azithromycin.

2.2 The Subcommittee noted that the Pharmaceutical Schedule currently provided for up to 5 days treatment with azithromycin for in effect any indication, with potentially unlimited duration treatment for specific indications on endorsement (as detailed in the Schedule).

2.3 The Subcommittee further noted its December 2014 recommendation that short courses of azithromycin of 5 days treatment be restricted to *Mycoplasma genitalium* infection when first line treatments have failed, and to treatment of pertussis and chlamydia. Members noted the December 2014 recommendation for longer courses of azithromycin being restricted to:

- Patients who have received a lung transplant and require treatment of prophylaxis for bronchiolitis obliterans syndrome,
- Patients with cystic fibrosis (CF) with 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 three acute admissions to hospital for treatment of infective respiratory exacerbations within a 12 month period.

2.4 Members noted that, following the receipt of the Subcommittee's 2014 clinical advice and its subsequent ratification by PTAC, in May 2016 PHARMAC had consulted on amending the listing of azithromycin. The Subcommittee noted that, following this consultation, PHARMAC had received approximately 20 consultation responses.

2.5 Members further noted that PHARMAC staff had sought PTAC's advice on those consultation responses at PTAC's August 2016 meeting. The Subcommittee noted draft PTAC minutes relating to that discussion and the resultant draft PTAC recommendations, which included a recommendation not to progress the Anti-infective Subcommittee's proposal to restrict 5-day azithromycin to specific indications (see paragraph 4.3), and PTAC's recommendation that the Anti-infective Subcommittee further discuss the use of azithromycin for 5 days treatment at the Subcommittee's next meeting.

2.6 The Subcommittee considered it clinically reasonable to restrict the use of azithromycin due to the increasing number of prescriptions and the large potential for antimicrobial resistance with this antibiotic. The Subcommittee noted that there currently is no mechanism to restrict short courses of azithromycin for any indication. The Subcommittee stressed that azithromycin usage does drive antimicrobial resistance, and considered azithromycin is currently being used in general practice far beyond the restricted indications that have been proposed. The Subcommittee also considered that there was anecdotal evidence suggesting appreciable misuse of azithromycin in eye infections.

2.7 The Subcommittee considered that PTAC's recommendation not to progress the Subcommittee's proposal (restricting 5-day treatment to specific indications) did not address the inappropriate usage of azithromycin. The Subcommittee, however, struggled to find an appropriate strategy that would address inappropriate usage and provide clinically appropriate access to azithromycin. With the recognition that respiratory tract infections are driving the inappropriate azithromycin usage, the Subcommittee **recommended** that funded use of the pertussis indication be further restricted to under the age of four years.

2.8 The Subcommittee requested long term ESR data regarding resistance patterns for Group A Streptococcus for discussion at the Subcommittee's next meeting. In addition, it requested data on increasing resistance to macrolides by pneumococcal and gonococcal isolates. The Subcommittee also requested any available usage data comparing hospital with community use of this agent.

2.9 The Subcommittee noted that PTAC, in its draft August 2016 minutes, had requested the Subcommittee review the retrospective longitudinal follow-up study by Sampson et al. (Resp Medicine 2016:117:1-6) on the long-term effects of azithromycin in patients with CF, which had reported no observed clinical benefits of low-dose azithromycin after one year of treatment in young CF patients. The Subcommittee **recommended** that ongoing funding of azithromycin beyond 12 months should be restricted for CF patients to those patients who have demonstrated clinical benefit of treatment to their first 12 months of treatment. Before progressing this recommendations, the Subcommittee **recommended** that the Respiratory Subcommittee review the long term effectiveness of azithromycin in the CF population and clarify if they believe it would be possible to restrict the long term use of azithromycin in CF.

2.10 The Subcommittee noted the draft minute from PTAC's August discussion on its role in relation to antimicrobial stewardship (AMS).

> (Draft) PTAC August minutes:
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> 14.18 The Committee noted its role in antimicrobial stewardship (AMS) within PHARMAC, and in turn PHARMAC's role within wider efforts by the heath sector to improve AMS, particularly the national antimicrobial resistance (AMR) framework work led jointly by the Ministry of Health and the Ministry for Primary Industries. The Committee considered that it is not currently its role to determine which specific medications should be used in preference to others as a result of AMS, particularly given inter-regional variation in microbial sensitivity and antimicrobial protocols, rendering specific funding restrictions problematic when on a PHARMAC-funding national scale.
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> 14.33 The Committee noted again the antimicrobial stewardship work currently being co-led by the Ministry of Health and the Ministry for Primary Industries which PHARMAC staff are participating in. The Committee considered that valuable feedback in the form of consultation responses were being provided by DHB antimicrobial stewardship committees. PTAC considered that these DHB antimicrobial stewardship committees should be able to use a national funding framework and apply their own regional variations. The Committee considered that the consultation had highlighted an important need for PHARMAC to continue its engagement with the Ministry of Health and other organisations to foster AMS leadership.

2.11 In relation to PTAC's statement drafted to date that "The Committee considered that it is not currently its role to determine which specific medications should be used in preference to others as a result of AMS", the Subcommittee voiced very clearly that it, as a subcommittee, should be taking on this AMS role, as no other mandated body is currently undertaking this task. As a result, the Anti-infective Subcommittee and PTAC may view AMS differently. The Subcommittee considered that AMS issues are very important to consider when making recommendations to PHARMAC. The Subcommittee noted that both Subcommittees and PTAC are required to make recommendations under PHARMAC's Factors for Consideration. The Subcommittee reasoned that AMS is reflected in the Factors when considering the benefits and risks to wider society and there were consequent risks to health sector services and costs from increasing AMR, and as such AMR considerations are integral to assessing such proposals.

2.12 The Subcommittee noted the AMS work led jointly by the Ministry of Health and the Ministry for Primary Industries. Members recognised that they were not represented within the current initiatives membership. The Anti-infective Subcommittee members identified that the successful implementation of the AMS framework requires a body to be mandated to make national AMS decisions and recognises that it has the skills to take on this task. Members considered that it is imperative that PHARMAC and the Subcommittee has the opportunity to provide input into any national discussions on AMS.

3 Levofloxacin

Recommendation

3.1 The Subcommittee **recommended** that the proposal for funding levofloxacin for second line *H. pylori* eradication be declined.

Discussion

3.2 The Subcommittee considered an application generated by PHARMAC staff to fund levofloxacin as a second line treatment for *Helicobacter pylori* infection. Members noted that the discontinuation of bismuth compounds and tetracycline in New Zealand prior to 2012 has led to an absence of appropriate second line therapies for resistant *H. pylori* which prompted the Gastrointestinal Subcommittee, at its April 2012 meeting, to recommend that PHARMAC pursue further suppliers of tetracycline and bismuth. Members noted however, that the ongoing availability of bismuth is very unreliable and PHARMAC was now seeking an alternative pharmaceutical for second line *H. pylori* treatment combinations.

3.3 The Subcommittee noted that the Gastrointestinal Subcommittee had noted it would be interested in levofloxacin, a broad-spectrum fluoroquinolone, for the

second line treatment of patients with *H. pylori*. Members noted that levofloxacin was not currently registered in New Zealand, however, recently a supplier had indicated to PHARMAC that it would be willing to supply levofloxacin. Members noted that PHARMAC staff now sought advice from the Subcommittee about the possible listing of levofloxacin.

3.4 The Subcommittee considered that *H. pylori* affects approximately 50% of the world's population. Members noted that Asian, NZ Māori and Pacific Island populations have higher rates of *H. pylori* infection rates compared with other ethnicities. Members considered that there was evidence of emerging resistance to first line treatments (clarithromycin and metronidazole). The Subcommittee considered that adherence to treatment was likely a contributing factor to emerging resistance and currently there is less than a 80% success rates with first line treatment. The Subcommittee considered that currently around 46 patients per month are prescribed second line treatment in New Zealand.

3.5 The Subcommittee considered that there is a lack of robust New Zealand *H. pylori* prevalence and resistance data. Members also considered that any recommendation to fund a new antibiotic in New Zealand required careful consideration of regional resistance patterns and that it would be reluctant to recommend funding a new antibiotic without this information. Members noted that there was widespread concern about emerging quinolone resistance.

3.6 The Subcommittee queried the inability of PHARMAC to source a suitable bismuth containing compound for New Zealand given that international guidelines feature bismuth in a good proportion of treatment protocols. The Subcommittee **recommended** that PHARMAC staff review all options for sourcing bismuth for the New Zealand market.

3.7 The Subcommittee **recommended** that PHARMAC staff seek advice from Associate Professor Dr Alan Fraser, Gastroenterologist, member of PTAC and Chair of the Gastrointestinal Subcommittee, regarding available NZ data on *H. pylori* resistance patterns and treatment failure rates, current first line treatment numbers and first line and second line treatment failure rates. The Subcommittee were also interested in an evidence comparing levofloxacin with current second line treatment options in New Zealand and requested clarification of what the current recommendations were for second line treatment in NZ in the absence of bismuth.

3.8 The Subcommittee discussed the role of rifabutin as part of combination treatment regimens in *H. pylori* treatment and considered that although resistance figures are relatively low, the risks associated with toxicity and the need for it to be preferably reserved for multi drug resistant tuberculosis meant it was likely not an appropriate *H. pylori* treatment choice.

3.9 The Subcommittee **recommended** that the application should be referred back to the Gastrointestinal Subcommittee for further advice and that it be brought back to the Anti-infective Subcommittee for review once the issues outlined above had been clarified.

4 Tenofovir for HIV and HBV infection and entecavir for HBV

4.1 The Subcommittee reviewed a paper from PHARMAC staff regarding the funding of Tenofovir disoproxil fumarate (Viread) for Hepatitis B (HBV) and HIV treatment. Members noted that there were a number of patents associated with the Viread brand of tenofovir which were due to expire. Members noted that PHARMAC staff were considering what commercial activities could be initiated in this area. The Subcommittee noted that these activities could affect both the hepatitis B and HIV treatment markets. Members noted that PHARMAC staff sought advice from the Subcommittee on the activities and the potential opportunities that may arise as a result of them.

4.2 The Subcommittee noted the availability of alternative salts of tenofovir disoproxil fumarate being tenofovir disoproxil maleate and tenofovir disoproxil succinate. The Subcommittee considered that once these salts were registered by Medsafe with tenofovir disoproxil fumarate as the reference product they would be considered clinically equivalent to tenofovir disoproxil fumerate and could be used interchangeably for treatment of Hepatitis B and HIV.

Note: reference to tenovofir in the subsequent minutes includes tenofovir disoproxil fumarate and other tenofovir alternative salt forms that have tenofovir disoproxil fumarate as its reference product.

4.3 The Subcommittee considered that there was no clinical reason for tenofovir not to be a first line therapy for the treatment of chronic HBV (CHB) for patients meeting the Special Authority entry criteria excluding those that have an allergy, intolerance or resistance. The Subcommittee noted that HBV resistance to tenofovir has not been observed in any patient to date. The Subcommittee considered that the number of CHB patients who would not be suited to tenofovir as a first line agent would be very small. The Subcommittee considered that there were no additional clinical benefits for CHB provided by entecavir compared with tenovofir.

4.4 The Subcommittee considered it would be clinically acceptable to switch CHB patients receiving entecavir to tenofovir. Members also considered that in a scenario where tenofovir was a first line treatment it would also be clinically acceptable to switch CHB patients to entecavir as a first line treatment, provided they were not resistant to entecavir or lamivudine and were unlikely to become pregnant or be breastfeeding.

4.5 The Subcommittee considered that patients could readily be switched from entecavir to tenofovir directly without a clinically managed transition period and with no risk of biological rebound or virologic breakthrough. The standard PHARMAC market transition period would be acceptable for a switch between entecavir and tenofovir. Members considered that patient switching could be overseen or managed by a specialist, nurse-led clinic or their general practitioner and there would not be a requirement for any specific monitoring. The only exceptions would be rare cases of multidrug resistance whereby patients may require specialist involvement and patients at risk of renal failure who would require additional monitoring.

4.6 The Subcommittee considered that educational resources aimed at primary care would be beneficial during drug transitioning focusing on treatment guidelines, resistance potential and efficacy of the antiviral agents.

4.7 The Subcommittee discussed resistance rates between different nucleos(t)ides. The Subcommittee noted that lamivudine has high rates of resistance that can result in cross resistance with other oral therapies and adefovir has inferior antiviral activity with increased rates of resistance and renal disease with long-term use. Members noted that tenofovir exhibited markedly lower resistance rates compared with other treatments and considered that, at present, tenofovir was not associated with first or second line virologic breakthrough. Members considered that tenofovir monotherapy was effective in lamivudine, adefovir, entecavir and lamivudine/adefovir resistance HBV. The Subcommittee considered that entecavir and tenofovir were clinically superior oral treatments for CHB and use of either should be encouraged over adevofir and lamivudine.

4.8 The Subcommittee considered that the appropriate algorithms for the treatment of cirrhotic and non-cirrhotic chronic HBV were as per the Asian Pacific Association for the Study of the Liver (APASL), American Association for the Study of Liver Diseases (AASLD) and the European Association of the Study of Liver (EASL) guidelines.

4.9 The Subcommittee discussed PHARMAC running a competitive process for funding of either entecavir or tenofovir to be the funded first line CHB treatment option and considered that there were no clinical issues that should inhibit competition in the CHB market.

4.10 The Subcommittee **recommended** that if entecavir was selected as the funded first line treatment patients who are allergic or intolerant to entecavir should also be able to access tenofovir and vice versa. Members noted that in the event that entecavir was selected as the first line funded treatment then tenofovir should remain funded as a first line treatment option for pregnant or breastfeeding patients as entecavir is not clinically appropriate in these patients.

4.11 The Subcommittee further **recommended** that access to tenofovir should be widened to include all women of child bearing potential who need treatment for chronic Hepatitis B with a high priority. Women of child bearing potential is defined as all women between the age of 15 and 45 who are premenopausal and have not undergone surgical sterilization.

4.12 The Subcommittee noted summary evidence from a number of studies that supported entecavir as a more potent agent than lamivudine for preventing HBV reactivation and hepatitis in surface antigen negative/core antibody positive patients receiving R-CHOP for lymphoma (Perillo RP et al. Gastroenterol 2015;148:221-44). Members, noted that there was not specific data for the use of tenofovir in this setting but considered it likely to be similar to entecavir. The Subcommittee **recommended** that PHARMAC considered widening access to entecavir or tenofovir for the prevention of HBV reactivation in surface antigen negative/core antibody positive patients receiving rituximab for malignancy should it obtain significant price discounts as a result of commercial activities.