Anti-Infective Subcommittee of the Pharmacology and Therapeutics Advisory Committee (PTAC)

Meeting held on 2 November 2017

(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 2016.*

Note that this document is not necessarily a complete record of the Anti-Infective Subcommittee meeting; 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 was reviewed by PTAC at its meeting on 3 & 4 May 2018, the record of which is now available on the PHARMAC website.

Record of the Anti-Infective Subcommittee meeting held at PHARMAC on 2 November 2017

1 Matters Arising and Correspondence

Matters Arising

1. Amendment to SA criteria for lamivudine prophylaxis

1.1 The Subcommittee reviewed a request from a clinician to amend the SA criteria for prophylactic lamivudine for patients receiving rituximab for any indication, not just for malignancy.

1.2 Members considered that lamivudine should be open listed, with initial prescribing restricted to, or on the recommendation of, a specialist as per the current funded prescribing restrictions, and with renewals by any relevant practitioner. The Subcommittee considered that open listing of lamivudine would lead to 40 to 60 additional patients per year accessing treatment.

2. Antimicrobial resistance

1.3 The Subcommittee noted that the Ministry of Health had released the New Zealand Antimicrobial Resistance Action Plan in August 2017.

Correspondence

1. Moxifloxacin

a. Amendment to SA criteria for Mycoplasma genitalium

1.4 The Subcommittee noted that PHARMAC receives a large number of Special Authority waivers for moxifloxacin for patients that have *Mycoplasma genitalium* with requests to waive the requirement for azithromycin to have been tried and failed for patients who have laboratory confirmed macrolide resistant infection.

1.5 Members considered that the SA criteria be should amended as per the request and recommended that prescribing be restricted to, or on the recommendation of, sexual health physicians. The Subcommittee agreed that the SA criteria should be amended as follows, with the same criteria for renewals:

Initial application — (*Mycoplasma genitalium*) **only from a sexual health physician or Practitioner on the recommendation of a sexual health physician** ~~from any relevant practitioner~~. Approvals valid for 1 month for applications
meeting the following criteria:
All of the following:

1.1 Has nucleic acid amplification test (NAAT) confirmed *Mycoplasma genitalium* **and is symptomatic***; and

1.2 Either:

1.2.1 Has tried and failed to clear infection using azithromycin; ~~and~~ **or**

1.2.2 Has laboratory confirmed azithromycin resistance.

1.3 Treatment is only for 7 days.

b. Amendment to SA criteria for tuberculosis

1.6 The Subcommittee reviewed a request from a Paediatric Infectious Disease Team and a clinician to amend the SA for moxifloxacin for children under 5 years of age who have been exposed to multi-drug resistant tuberculosis (MDR-TB). Members noted that moxifloxacin is the only agent and treatment of choice for the management of exposure to MDR-TB in children in New Zealand because it can be made into an elixir.

1.7 The Subcommittee **recommended** that funded access to moxifloxacin be widened to children under 5 years of age who have had close contact with confirmed MDR-TB cases with a high priority.

2. Request for prescriber consistency for protionamide and para-amino salicylic acid

1.8 The Subcommittee reviewed a request from a clinician for consistency regarding prescribers for medications listed in the Antituberculotics and Antileprotics subsection of the Pharmaceutical Schedule.

1.9 Members agreed that prescribers should be consistent for these medications and **recommended** that prescribing for both protionamide and para-amino salicylic acid should be by, or on the recommendation of, an ID specialist, clinical microbiologist, or respiratory specialist.

3. Correspondence regarding clarification of restrictions to oseltamivir for influenza

1.10 The subcommittee reviewed requests from the an Antimicrobial Stewardship Committee and a DHB Antimicrobial Stewardship and Pharmacy and Therapeutics Committees regarding the supply of oseltamivir for Influenza in Section H to patients being discharged from hospital. Members noted that PHARMAC had provided formal clarification to DHB Chief Pharmacists regarding the restriction of oseltamivir and zanamivir, and whether Rule 8 would apply, as below:

> "The oseltamivir restriction states that it should be used only for a hospitalised patient. This specific restriction prevails over Rule 8, therefore oseltamivir should not be dispensed into the community. This requirement for the patient to be hospitalised also means that patients commenced on oseltamivir in hospital should not receive the unfinished portion of a course to take home."
>
> "The intent of the restriction is not to create a situation where a patient remains hospitalised in order to finish a course but is based on the premise that if the patient has recovered sufficiently for discharge, then further treatment (or prophylaxis) with oseltamivir is unnecessary."

1.11 The Subcommittee noted that these restrictions followed previous PTAC advice, and PHARMAC had added notes to the listing of oseltamivir and zanamivir in Part II of Section H of the Pharmaceutical Schedule from 1 September 2017 as follows:

> Note: The restriction on the use of oseltamivir to hospitalised patients means that supply into the community under Rule 8 of Section H is not permitted.
>
> Note: The restriction on the use of zanamivir to hospitalised patients means that supply into the community under Rule 8 of Section H is not permitted

1.12 Members considered that there was no additional cost associated with sending patients home with the rest of the dispensed course of treatment, and considered that there was circumstantial evidence of benefit to completing the treatment course with oseltamivir. The Subcommittee agreed that continuing the treatment course would be aligned with international guidelines and **recommended** that Rule 8 in Section H apply, and the restriction to oseltamivir and zanamivir be altered to reflect this.

4. Request to widen funded access of albendazole for giardiasis

1.13 The Subcommittee reviewed a request from a supplier, to widen funded access of albendazole for the treatment of giardiasis. Members considered that both metronidazole and ornidazole are effective for the treatment of giardiasis, although albendazole may be appropriate in cases of resistance. The Subcommittee considered that the number of resistant cases that would require albendazole would be at most one or two per year, and that there was no evidence from NPPA applications that there was an unmet need for giardiasis treatment. Members **recommended** that albendazole not be listed on the Pharmaceutical Schedule for the treatment of giardiasis.

5. Amendment to SA criteria for fluconazole syrup

1.14 The Subcommittee reviewed a request from a Paediatric Infectious Diseases Team and a clinician to amend the SA criteria for fluconazole syrup to include treatment of non-invasive fungal infections of the urine or skin in immunocompetent children and infants unable to swallow tablets. Members noted that fluconazole tablets are available for non-systemic infections in adults and older children.

1.15 The Subcommittee considered that removing the SA criteria would lead to an increased uptake of fluconazole syrup in the elderly, and recommended that the SA criteria be amended to widen funded access for immunocompetent young children with serious *Candida* fungal infection who are unable to swallow tablets.

6. Amendment to SA criteria for tenofovir disoproxil fumarate

1.16 The Subcommittee reviewed correspondence from a clinician regarding the requirement for patients to have decompensated cirrhosis and a Mayo score greater than 20 to access funded tenofovir disoproxil fumarate for the treatment of chronic hepatitis B. Members advised that the term ‘Mayo score’ is no longer used and noted that tenofovir disoproxil fumarate should be available for treatment of patients with acute or chronic liver failure.

7. Request for cefalexin grans for oral liquid to be subsidised on a Practitioner’s Supply Order

1.17 The Subcommittee reviewed a request for cefalexin suspension to be available on a Practitioner’s Supply Order (PSO) so it is available following out of hours consultations for children with infected eczema. Members considered that there was a benefit to having Cefalexin available after hours and **recommended** that it be available on a PSO.

8. Request for restrictions for fluoroquinolones

1.18 The Subcommittee reviewed a request from the a Regional Community Antimicrobial Stewardship Committee to restrict funded access to a number of fluoroquinolones in the

community, including norfloxacin, ciprofloxacin and ciprofloxacin eye drops. Members noted that ASC requested the following restrictions to Section B of the Pharmaceutical Schedule:

- moxifloxacin: continue current restrictions
- norfloxacin: in cases of urinary tract infections with proven resistance
- ciprofloxacin: clinically significant *P.aeruginosa* infections or *N.gonorrhoeae* infections, when susceptibilities are known, requiring Infectious Disease/microbiologist specialist approval, and other infections on recommendation of Infectious Disease/microbiologist specialists
- ciprofloxacin eye drops: bacterial keratitis
- other infections recommended by an infectious disease specialist

1.19 The Subcommittee agreed that it was necessary to preserve this group of antibiotics for indications where it was required. Members noted that norfloxacin prescribing was by endorsement, and recommended that a further amendment be made restricting access if unresponsive to a first line AND a second line agent.

1.20 Members discussed indications that require ciprofloxacin, and considered that use could be reduced by amending subsidy to be by endorsement. The Subcommittee **recommended** that ciprofloxacin in the Section B of the Pharmaceutical Schedule be recommended for patients with any of the following: i) microbiologically confirmed and clinically significant and susceptible pseudomonal infection; or ii) prostatitis with proven resistance to other first and second line agents; or iii) pyelonephritis with proven resistance to other first and second line agents; or iv) clinically significant and susceptible gonorrhoea; or v) other indications on recommendation of a clinical microbiologist/infectious disease specialist or public health physician.

1.21 The Subcommittee considered that the restrictions for moxifloxacin and subsidy by endorsement for ciprofloxacin eye drops were appropriate and did not think any further restriction were necessary.

2 Pre-exposure prophylaxis for prevention of HIV (PrEP)

Background

2.1 The Subcommittee reviewed a funding application from the New Zealand AIDS Foundation to widen funding of tenofovir disoproxil with emtricitabine (TD/FTC) for HIV pre-exposure prophylaxis (PrEP).

Recommendation

2.2 The Subcommittee **recommended** that tenofovir disoproxil with emtricitabine (TD/FTC) be listed on the Pharmaceutical Schedule with a high priority for pre-exposure prophylaxis (PrEP) for individuals at a high risk of contracting HIV.

Discussion

2.3 The Subcommittee reviewed the clinical trial data of TD/FTC for PrEP in the following studies:

- Grant et al. N Engl J Med. 2010; 363(27):2587-99,
- Baeten JM et al. N Engl J Med. 2012;367(5):399-410,
- Baeten JM et al. Lancet Infect Dis. 2014;14(11):1055-64,
- McCormack et al. Lancet. 2016;387(10013):53-60, and
- Molina et al. N Engl J Med. 2015;373(23):2237-46.

The Subcommittee also considered information provided in a Cochrane Review on Antiretroviral PrEP for preventing HIV in high-risk individuals (Owkwundu et al. The Cochrane Library, 2012).

2.4 The Subcommittee considered that there was good quality evidence to support the use of TD/FTC for PrEP to prevent infection in individuals at a high risk of contracting HIV. The Subcommittee noted that the relevant clinical trial data indicated that that daily TD/FTC reduced the relative risk of acquiring HIV infection by 44-86% compared with placebo or no prophylaxis. Members noted that the risk reduction was not very high in the IPrEX study (Grant et al. N Engl J Med. 2010; 363(27):2587-99), but was significantly higher in more recent studies. Members noted that efficacy was strongly correlated to adherence to TD/FTC and in a sub-study of the IPrEX trial, the protective efficacy of PrEP increased to over 96% for those with TD/FTC levels suggested that they took at least 4 doses per week (Anderson et al. Sci Trans Med, 2012).

2.5 The Subcommittee discussed the Auckland Sexual Health Service PrEP Trial, an open-label, single-arm evaluation study run in Auckland that is still in progress. Enrolments for the trial started in February 2017, and currently 145 of the 150 planned participants have been enrolled. Members noted the inclusion criteria for the trial which was targeted towards gay or bisexual men at a high-risk of contracting HIV. Members noted that rates of sexual transmitted infections were high in participants, and 23% had an STI at enrolment. No HIV seroconversion have been observed to date (unpublished data).

2.6 The Subcommittee considered that there were no other medical treatment options for HIV PrEP. Members considered that while condoms might be considered an alternative, attitudes regarding condoms have changed since HIV is now considered a treatable disease. Members noted that despite the toolbox of strategies available for reducing HIV transmission in New Zealand, including condoms, post-exposure prophylaxis, and early treatment of HIV following diagnosis, new HIV diagnosis rates have been increasing and 2016 saw the highest number of new diagnosis ever in New Zealand. The Subcommittee considered that TD/FTC for PrEP would provide benefit if used by those individuals that do not regularly use condoms and are at a high-risk of contracting HIV.

2.7 The Subcommittee reviewed the groups of individuals considered at a high risk of contracting HIV according to PrEP clinical trial inclusion criteria, the Auckland Sexual Health Service PrEP Trial and the clinical guidelines proposed by the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) (Wright et al. J Vir Erad. 2017;3(3):168). Members noted that men who have sex with men (MSM) and women who are regular sexual partners of an HIV positive person (not on treatment and/ or with detectable viral load) with whom condoms have not been consistently used were considered at high risk.

2.8 The Subcommittee discussed the risks and benefits of an open listing. Members considered that an open listing would attract interest from people who had no risk or were at a low–medium risk and were anxious regarding their risk of contracting HIV infection. The Subcommittee noted that restricted access would help in the management of patient's sexual health and in many cases, unnecessary concern regarding their risk of HIV infection. Members emphasised that benefit of PrEP would be best realised, including lower rates of infection for the individual and reduced transmission rates in New Zealand, if access was restricted to individuals that were at a high-risk of infection.

2.9 The Subcommittee considered that should TD/FTC be funded for PrEP, there would not be an increased risk of drug-resistant HIV nor an increased risk of drug-resistance for sexually transmitted infections. Members noted that the risk of selection for drug resistant HIV was more theoretical than real, and cases of drug-resistant HIV detection were in individuals that had an acute HIV infection at the time of enrolment in PrEP. Members noted that commencement on PrEP could encourage riskier behaviour that could increase the rates of sexually transmitted infections. The Subcommittee considered that a requirement for 3-monthly screens for sexually transmitted infections for eligibility for PrEP would mean that patients would be tested and treated more often, reducing the risk of spreading asymptomatic sexually transmitted infections. Members noted that in the longer term there may be an opportunity to reduce STI rates, and associated costs, through early detection and treatment. Members had no concerns regarding the risk of further complications, including renal impairment or bone density loss for patients on daily TD/FTC for PrEP.

2.10 The Subcommittee considered that the cost utility analysis would be highly dependent on HIV incidence rates and noted that in Auckland DHB, the incidence in MSM is estimated at 0.2 per 100 person years. Members noted that TD/FTC would be cost effective if PrEP eligibility was restricted to individuals at a high risk of infection and noted cost-effectiveness estimates that the QALYs gained would be approximately 35 per $1 million invested if PrEP was funded for all MSM, and would be in the range of 170 QALYs per $1 million invested to cost saving if funding was targeted to high-risk individuals.

2.11 The Subcommittee noted that a number of generic emtricitabine with tenofovir disoproxil products that are indicated for PrEP are registered with Medsafe. Members did not express any concern regarding the use of different salt forms of tenofovir disoproxil, and suggested that PHARMAC staff check the current registration of generic tenofovir disoproxil salt forms indicated for PrEP in Europe.

2.12 Members noted that there would be an increase in the resource requirements in sexual health clinics. The Subcommittee considered that monitoring of sexually transmitted diseases would increase testing volumes in laboratories, but this would be relatively low number overall and unlikely to have an appreciable impact.

2.13 The Subcommittee considered that the New Zealand AIDS Foundation estimate of 4000 patients that would be considered at a high-risk of HIV infection and therefore eligible for PrEP was a good estimate.

2.14 The Subcommittee considered that initial treatment should be restricted to, or on the recommendation of, sexual health physicians and infectious disease specialists, and considered that renewals could be prescribed by general practitioners trained in the prescribing and management of patients on TD/FTC for PrEP.

2.15 Members considered that funded access to PrEP be restricted to MSM, or transgender females, are HIV negative and in the last three months met any of the following: are likely to have multiple episodes of receptive condomless anal intercourse, have a regular partner with HIV infection (either not on treatment or with a detectable HIV viral load), have had at least one episode of receptive condomless anal intercourse with a casual male partner, have had a diagnosis of rectal chlamydia/gonorrhoea or any infectious syphilis, have used methamphetamine. The Subcommittee agreed with international guidelines suggesting that individuals that use methamphetamine are considered at a higher risk of contracting HIV due to a number of reasons, including increasing risky behaviour, the higher prevalence of methamphetamine use in MSM and risk associated with needle sharing.

2.16 The Subcommittee also recommended that approvals be valid for three months, with a requirement that patients undergo laboratory testing for HIV, syphilis, a full STI screen and renal testing to qualify for renewal. Members also considered that patients be counselled regarding ways to reduce their risk of contracting HIV. Members noted that PHARMAC would liaise with appropriate Subcommittee members following the meeting to refine Special Authority criteria.

3 Any other business

Horizon scanning

3.1 The Subcommittee noted that letermovir was an antiviral drug that was being developed for prophylaxis/treatment of cytomegalovirus infections and noted that MSD is planning to submit it to Medsafe for registration shortly.

3.2 The Subcommittee noted that PHARMAC has representation on the Health Antimicrobial Resistance Coordination Group. Members requested that antimicrobial stewardship be a standing item at every Subcommittee meeting and suggested that members could review a subgroup as provided in the Therapeutic Group Review and discuss whether specific Special Authority criteria are still appropriate.