Record of the Anti-Infective Subcommittee of PTAC Meeting held via videoconference on 22 September 2020

Anti-infective Subcommittee records 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; only the relevant portions of the meeting record 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.

PTAC Subcommittees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Subcommittee meeting will be reviewed by PTAC at its February 2021 meeting.

PTAC Subcommittees and PTAC may differ in the advice they provide to PHARMAC, including recommendations' priority, due to the committees' different, if complementary, roles, expertise, experience, and perspectives.

PHARMAC is not bound to follow the recommendations made below. Applications are prioritised by PHARMAC against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or PTAC Subcommittees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

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Present from the Anti-infective Subcommittee:
Sean Hanna (Chair)
Anja Werno
Eamon Duffy
Ed Gane
Emma Best
Graham Wills
Howard Wilson
Jane Morgan
James Chisnall
Rhiannon Braund
Simon Briggs
Steve Chambers
Tim Matthews

1. The role of PTAC Subcommittees and records of meetings

This meeting record of the Anti-infectives Subcommittee of PTAC is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016, available on the PHARMAC website at https://www.pharmac.govt.nz/assets/ptac-terms-of-reference.pdf.

The Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of PTAC Subcommittees and PTAC.

Conflicts of Interest are described and managed in accordance with section 7.2 of the PTAC Terms of Reference.

The Anti-Infective Subcommittee is a Subcommittee of PTAC. The Anti-Infective Subcommittee and PTAC and other PTAC Subcommittees have complementary roles, expertise, experience, and perspectives. The Anti-Infective Subcommittee and other PTAC Subcommittees may therefore, at times, make recommendations for treatments for anti-infectives that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at

times, make recommendations for treatments for anti-infectives that differ from the Anti-Infective Subcommittee's, or PTAC Subcommittees may make recommendations that differ from other PTAC Subcommittees'.

PHARMAC considers the recommendations provided by both the Anti-Infective Subcommittee and PTAC and any other relevant PTAC Subcommittees when assessing applications for treatments for Infections.

2. Summary of recommendations

2.1 The Subcommittee **recommended** that, based on the updated guidelines, linezolid be funded with a **high priority** for the treatment of MDR-TB. The Subcommittee considered that there is an unmet health need in patients with MDR-TB and considered that linezolid should be listed in Section B subject to the following Special Authority criteria:

> **Special Authority for Subsidy**
> Initial application – (tuberculosis - multidrug-resistant). From any relevant practitioner. Approvals valid for 18 months for applications meeting the following criteria:
> Both:
> 1. The patient has multidrug-resistant tuberculosis (MDR-TB); and
> 2. The Ministry of Health's Tuberculosis Clinical Network has reviewed the patient case and recommends linezolid as part of the treatment regimen.

2.2 The Subcommittee **recommended** that the application for the rifampicin/isoniazid/ pyrazinamide/ethambutol fixed dose combination (FDC) tablet be funded with a **high priority**, within the context of anti-infective treatments.

2.3 The Subcommittee **recommended** that letermovir for cytomegalovirus infection prophylaxis in haematopoietic stem cell transplant patients be listed with a **low priority** within the context of treatments for infections, subject to the following Special Authority criteria:

> **Special Authority for Subsidy**
> Initial application only from a haematologist or infectious disease specialist; approvals valid for four months for applications meeting the following criteria:
> All of the following:
> 1 Patient must have undergone an allogeneic haematopoietic stem cell transplant; and
> 2 The patient must have confirmed presence of cytomegalovirus-specific antibodies; and
> 3 Treatment must commence within 28 days of an allogeneic haematopoietic stem cell transplant; and
> 4 Maximum treatment duration of one hundred days.

2.4 The committee **recommended** that Bictegravir 50 mg/Emtricitabine 200 mg/Tenofovir alafenamide 25 mg (Biktarvy) be listed as **cost neutral** to the weighted price of all currently funded HIV treatments, within the context of treatments for infections.

3. Record of Subcommittee meeting held Friday, May 10, 2019

3.1 The Subcommittee noted the record of the previous meeting that took place on 10 May 2019. The Subcommittee noted the following minutes, with any comments and concerns raised by the Subcommittee.

4. Therapeutic Group and NPPA Review

4.1. The Subcommittee noted the main contributors to the gross pharmaceutical expenditure in the Infections – Agents for Systemic Use therapeutic group.

Anthelmintics

4.2. The Subcommittee noted that the currently funded brand of mebendazole 100 mg tablets will be discontinued by the supplier from March 2021. If another brand of tablets is not available, members considered mebendazole 500 mg and pyrantel 100 mg chocolate squares would be suitable alternatives for the treatment of threadworm.

Antibacterials

4.3. The Subcommittee noted that globally, countries are moving to a twice-daily formulation of cefaclor monohydrate 375 mg modified-release capsule. Members considered that the three-times-a-day and two-times-a day formulations could be used interchangeably and considered that the reduced dosing frequency would support better compliance. However, the Subcommittee considered that any future change to the twice-daily formulation may result in increased usage due to inappropriate prescribing. As such, members considered that further education such as through the Responsible Use provider would be needed to highlight the need for careful consideration of the antibiotic choices made. The Subcommittee considered that there would be no unmet health need if the three-times-a-day formulation were replaced with a two-times-a-day formulation in the future.

Macrolides

4.4 The Subcommittee considered the usage of azithromycin may continue to increase given that it can be prescribed for any indication for up to five days. Members noted its comparatively long half-life which contributes to the development of resistance. Members suggested that PHARMAC consider further restricting its use with subsidy by endorsement whereby the funding is restricted to use in pertussis or on the recommendation of an Infectious Disease (ID) physician or Clinical Microbiologist. Members also noted that the treatment can currently be prescribed for longer periods if the patient meets the Special Authority criteria for bronchiolitis obliterans syndrome, cystic fibrosis, atypical Mycobacterium infections or non-cystic fibrosis bronchiectasis. The Subcommittee considered that these exceptions for longer use remain appropriate.

Other antibiotics

4.5 The Subcommittee noted that PHARMAC temporarily removed the “Retail Pharmacy – Specialist” restriction from several pharmaceuticals including clindamycin in April 2020 in response to COVID-19. This change became permanent following a consultation process in June 2020, noting that PHARMAC intends to seek further advice on whether funding criteria targeting indications are required for some antimicrobial agents. Members noted that clindamycin is usually prescribed as a second-line option for bacterial vaginosis or as an alternative for prophylaxis of infective endocarditis prior to invasive dental procedures when allergic to penicillin. Members also noted that clindamycin is considered for the treatment of community acquired Methicillin-resistant Staphylococcus aureus (MRSA). However, Members considered that usage has increased since the widening of access and raised concerns that it would be inappropriate for clindamycin to be used as a first-line agent especially in conditions such as cellulitis. Members suggested that a note be added to help facilitate appropriate prescribing.

Penicillins

4.6. The Subcommittee reviewed the usage of amoxicillin with clavulanic acid and noted that its prescribing has not declined as much as anticipated over the past year. Members considered that amoxicillin with clavulanic acid is a broad spectrum antibiotic and should not be used as a first-line agent in primary care. Members considered that prescriber communication is needed to remind them of the need for careful consideration of the antibiotic choices made.

Hepatitis C treatments

4.7. The Subcommittee reviewed the monthly uptake of glecaprevir/pibrentasvir (Maviret) since its listing in February 2019. The Subcommittee noted the decreasing trend for its usage over the past 12 months. It was also noted that over the past three months there were about 50 new treatment initiations per month. Members considered that the reduced testing and treating in the community due to COVID-19 restrictions has resulted in such a low uptake during those months.

4.8. The Subcommittee noted that there is a significant increase in the treatment initiated in primary care setting, especially in the past few years as the pan-genotypic direct acting antivirals (DAA) has been funded.

4.9. The Subcommittee noted that, out of 3,200 patients treated with Viekira Pak, there are about 90 DAA failures. In contrast, out of 3,800 patients treated with Maviret so far, there are about 17 failures (less than 0.5%). Members noted that there could be an additional 10 to 20 DAA failures per year.

4.10. The Subcommittee considered that patients who complete a course of Maviret and do not achieve sustained virologic response (SVR) and have NS5A/NS3 resistance, have two salvage options available, one approved and the other “off-label”. As noted in the May 2019 meeting, the approved regimen consists of three DAAs, sofosbuvir/ velpatasvir/ voxilaprevir (Vosevi) and the other regimen is the addition of sofosbuvir to retrial of Maviret and ribavirin. Members noted that neither of the treatment options is currently funded.

4.11. Members considered that, as per the guidelines for cirrhotic DAA failures from the European Association for the Study of the Liver (EASL), compensated cirrhotic patients who failed DAA regimen with NS5A/NS3 resistance can be treated with either Vosevi for 12 weeks or Maviret with sofosbuvir for 12 weeks. Members also noted that compensated cirrhotic patients who failed on two or more DAA regimens can be treated with either Vosevi with ribavirin for 16 to 24 weeks or Maviret with sofosbuvir and ribavirin for 16 to 24 weeks.

4.12. Members considered that there is an unmet health need for the patients who complete a course of Maviret but do not achieve SVR and have NS5A/NS3 resistance. Members also considered that these patients could be considered under the Named Patient Pharmaceutical Assessment or for listing on the Pharmaceutical Schedule to enable treatment access.

Antituberculotics and Antileprotics

4.13. The Subcommittee noted that a funding application for bedaquiline for multidrug-resistant tuberculosis (MDR-TB) was considered by PTAC in February 2020.

4.14. The Subcommittee noted that PTAC recommended that bedaquiline be funded with a high priority for the treatment of multidrug-resistant tuberculosis (MDR-TB) based on

high health need and good evidence supporting the efficacy and safety of bedaquiline, subject to the following Special Authority criteria:

> **Special Authority for Subsidy**
> Initial application – (tuberculosis - multidrug-resistant). From any relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:
> Both:
> 1. The patient has multidrug-resistant tuberculosis (MDR-TB); and
> 2. The Ministry of Health's Tuberculosis Clinical Network has reviewed the patient case and recommends bedaquiline as part of the treatment regimen.

4.15. The Subcommittee note that before this recommendation could be progressed, it would be necessary to establish a suitable dispensing mechanism to enable the listing of bedaquiline for extensively drug resistant tuberculosis (XDR-TB). The Subcommittee noted that PHARMAC staff are currently exploring options that would make this listing possible.

4.16. The Subcommittee noted, that in making the high priority recommendation for bedaquiline, PTAC commented that it was important to consider the recent update in MDR-TB treatment guidelines from the World Health Organization. Members also noted that the guidelines recommend the use of three Group A agents: bedaquiline, linezolid and moxifloxacin or levofloxacin. However, Members noted that only moxifloxacin can currently be accessed through Section B of the Pharmaceutical Schedule and the remaining Group A agents are accessed through the Exceptional Circumstances framework.

4.17. The Subcommittee **recommended** that, based on the updated guidelines, linezolid be funded with a **high priority** for the treatment of MDR-TB. The Subcommittee considered that there is an unmet health need in patients with MDR-TB and considered that linezolid should be listed in Section B subject to the following Special Authority criteria:

> **Special Authority for Subsidy**
> Initial application – (tuberculosis - multidrug-resistant). From any relevant practitioner. Approvals valid for 18 months for applications meeting the following criteria:
> Both:
> 1 The patient has multidrug-resistant tuberculosis (MDR-TB); and
> 2 The Ministry of Health's Tuberculosis Clinical Network has reviewed the patient case and recommends linezolid as part of the treatment regimen.

4.18. The Subcommittee noted that levofloxacin is being prescribed with bedaquiline on many occasions as moxifloxacin causes QT prolongation and requested that PHARMAC consider its listing on the Pharmaceutical Schedule. Members also noted that there is currently no registered product for levofloxacin in New Zealand.

Urinary Tract Infections

4.19. The Subcommittee reviewed the usage information for agents used in the treatment of urinary tract infections, especially for nitrofurantoin, trimethoprim and norfloxacin.

4.20. The Subcommittee considered there were concerns about the decreasing usage of nitrofurantoin as it is the first-line agent for urinary tract infections (UTIs). Members linked this trend to a number of barriers including dosing frequency (i.e. four times daily) and lack of clarity with the current prescribing guidelines.

4.21. The Subcommittee considered the recommended dosing of the currently funded immediate-release nitrofurantoin is not ideal for patient compliance, especially when compared to the other available agents. Members considered that concerns about poor patient compliance may discourage the prescribers from prescribing nitrofurantoin and promote the use of other antibiotics which are less appropriate as an empiric first-line

treatment for UTI. As such, nitrofurantoin modified-release capsules, which have twice-daily dosing frequency, were recommended for listing on the Pharmaceutical Schedule by the Subcommittee at its November 2015 meeting and by PTAC at its February 2016 meeting. Members noted that PHARMAC included nitrofurantoin modified-release in the 2019/20 Invitation to Tender (ITT). Members considered that listing nitrofurantoin modified-release capsules would help manage the risk of antimicrobial resistance.

4.22. The Subcommittee considered that there was lack of clarify with the use of nitrofurantoin in renally impaired patients. Members noted that guidelines indicate that it is contraindicated if eGFR is less than 60 ml/minute/1.73 m^2, however, they consider that a review of such recommendation is needed as new evidence has emerged in the past few year. Members also considered that the current recommendations are not in keeping with other international regulators e.g. FDA or MHRA. Members noted that this was discussed by Medicines Adverse Reactions Committee at its March 2019 meeting, when it recommended that no change was needed. Members suggested that PHARMAC make a submission to MARC for their re-consideration of the latest evidence and review of the current recommendation.

4.23. The Subcommittee reviewed the usage of trimethoprim and indicated that they expected the decline to be larger. Members considered that the steady decline may be due to pharmacists supplying trimethoprim over-the-counter for eligible patients. Members also considered that it would be more useful if pharmacists could supply nitrofurantoin instead of trimethoprim and requested that PHARMAC work in partnership with the sector to support such change.

4.24. The Subcommittee reviewed the usage of ciprofloxacin and noted that it does not have any funding restrictions in place to minimise the inappropriate prescribing. Members considered that the note recommending its indications (i.e. pseudomonas infection, prostatitis, pyelonephritis, gonorrhoea) is not restrictive enough. As such, the Subcommittee recommended that ciprofloxacin either be restricted to subsidy by endorsement or by Special Authority criteria for the indications already listed.

4.25. The Subcommittee noted that the use of norfloxacin is currently funded only if a patient with UTI is unresponsive to a first-line agent or with proven resistance to first-line agents and the prescription is endorsed accordingly. Members noted their concerns regarding the increased usage of norfloxacin and considered that it is highly likely that inappropriate prescribing contributed towards the usage growth. Members suggested further restricting the access to norfloxacin by removing the current subsidy by endorsement and replacing it with the following Special Authority criteria:

> **Special Authority for Subsidy**
> Initial application – (uncomplicated urinary tract infection). From relevant practitioner. Approvals valid for 3 months for applications meeting the following criteria:
> Both:
> 1. Patient has an acute, symptomatic, bacteriologically-proven uncomplicated urinary tract infection (UTI); and
> 2. The bacteria, based on the microbiology report, is resistant to nitrofurantoin, trimethoprim, amoxicillin, amoxicillin-clavulanic acid and cefalexin; or
> 3. The patient has a contraindication or documented intolerance nitrofurantoin, trimethoprim, amoxicillin, amoxicillin-clavulanic acid and cefalexin.

5. Matters Arising and Correspondence

Fosfomycin

5.1. The Subcommittee noted that in May 2019, the Anti-Infective Subcommittee reviewed an application from Te Arai BioFarma for fosfomycin trometamol (fosfomycin) for the first-line treatment of uncomplicated urinary tract infections (UTIs). At that time, the Subcommittee noted that PHARMAC received two items of correspondence (March 2019 and April 2019) from the applicant regarding the proposed place of fosfomycin in therapy, with the second correspondence item requesting fosfomycin as a second-line option after nitrofurantoin failure or where there is a contraindication or intolerance to other treatment options. In May 2019, the Subcommittee had recommended that fosfomycin be funded for the treatment of uncomplicated UTIs with a high priority, subject to Special Authority criteria (for Section B) or Restriction criteria (for Section H) as detailed in the May 2019 record.

5.2. The Subcommittee noted that PHARMAC had received correspondence in July 2020 from Te Arai Biofarma, the supplier of UroFos (fosfomycin) following registration of this product. The Subcommittee noted that Te Arai Biofarma requested clarification on the recommended funding criteria for fosfomycin, including specific antibiotic treatments to be used for UTIs prior to use of fosfomycin; whether an endorsement was more appropriate than Restriction criteria; and proposing that urologists should be added as a prescriber type. In their correspondence, Te Arai Biofarma proposed the following endorsement for fosfomycin which the supplier considered would constrain fosfomycin to the third-line use in symptomatic, uncomplicated acute UTIs, which they believe is consistent with the Subcommittee's May 2019 recommendations:

- The bacteria, based on the microbiology report, is resistant to other **first line UTI** antibiotics including nitrofurantoin; or
- The patient has a contraindication or documented intolerance to **other first line** UTI antibiotics including nitrofurantoin.

5.3. The Subcommittee considered it important for the place of fosfomycin in the funded treatment paradigm for treatment of UTIs ensures its appropriate use in primary care and follows the principles of antimicrobial stewardship. The Subcommittee noted that there is data indicating *E. coli* has high resistance to trimethoprim and it is about 93% sensitive to cefalexin. The Subcommittee considered that fosfomycin may be the only effective agent available for the treatment of multidrug-resistant ESBL-producing Gram-negative organisms and considered that its use for *E. coli* with standard sensitivity may select for resistance to fosfomycin.

5.4. The Subcommittee considered that decisions regarding the use of fosfomycin or other agents for the treatment of UTIs to be guided by the results of susceptibility testing. The Subcommittee considered that, in line with its advice in May 2019, all of the following funded agents for which testing indicates bacterial sensitivity should be used prior to treatment with fosfomycin: trimethoprim, nitrofurantoin, amoxicillin, cefalexin, amoxicillin with clavulanic acid and norfloxacin.

5.5. The Subcommittee considered that the Special Authority criteria (for Section B) or Restriction criteria (for Section H) were more appropriate than endorsement and considered that it was not necessary to include urologists as prescribers for fosfomycin, noting that limiting to clinical microbiologist and infectious disease specialist would help to ensure appropriate use.

5.6. The Subcommittee considered that the criteria for fosfomycin for the first-line treatment of UTIs should be amended as follows for clarity (additions shown in **bold**, deletions shown in ~~strikethrough~~):

> **Special Authority for Subsidy**
> Initial application – only from clinical microbiologist or infectious disease specialist.
> All of the following:

1. Patient has an acute, symptomatic, bacteriologically-proven uncomplicated urinary tract infection (UTI); and
2. The bacteria, based on the microbiology report, is resistant to **trimethoprim, nitrofurantoin, amoxicillin, cefalexin, amoxicillin with clavulanic acid and norfloxacin** ~~all other antibiotics including nitrofurantoin~~; or
3. The patient has a contraindication or documented intolerance to **trimethoprim, nitrofurantoin, amoxicillin, cefalexin, amoxicillin with clavulanic acid and norfloxacin** ~~all UTI antibiotics including nitrofurantoin.~~

Note: Fosfomycin should not be used for first-line treatment. Upon request, microbiology should report fosfomycin sensitivity for patients with resistant infections.

Restricted
Initiation – On the recommendation of clinical microbiologist or infectious disease specialist.
All of the following:

1. Patient has an acute, symptomatic, bacteriologically-proven uncomplicated urinary tract infection (UTI); and
2. The bacteria, based on the microbiology report, is resistant to **trimethoprim, nitrofurantoin, amoxicillin, cefalexin, amoxicillin with clavulanic acid and norfloxacin** ~~all other antibiotics including nitrofurantoin~~; or
3. The patient has a contraindication or documented intolerance to **trimethoprim, nitrofurantoin, amoxicillin, cefalexin, amoxicillin with clavulanic acid and norfloxacin** ~~all UTI antibiotics including nitrofurantoin.~~

Practitioners' Supply Order (PSO)

5.7. The Subcommittee noted that in response to the COVID-19 pandemic, as a way to lower the risk of community transmission by reducing patient movement to have some of the prescriptions filled, the Primary Health Organisation Clinical Leads Forum requested PHARMAC to explore whether urban practices could apply the Practitioners' Supply Order (PSO) rules like rural practices or at least include cefalexin grans for oral liquid (25 mg per ml and 50 mg per ml), flucloxacillin (500 mg capsule) and valaciclovir (500 mg tablet) to the current PSO list.

5.8. The Subcommittee noted that PHARMAC considered factors such as the intent of the PSO rules, any unmet health need and whether the supply chain is robust enough to withstand any changes, especially when it may be already under pressure due to the global pandemic. After careful consideration, PHARMAC decided to add flucloxacillin 500 mg capsule to the PSO list as this would align with the intent of the PSO rules for immediate treatment in clinic and align with dosing for treatment of susceptible infections.

5.9. The Subcommittee noted that PHARMAC has decided not to progress with addition of cefalexin and valaciclovir to the PSO list at this time.

5.10. The Subcommittee requested that PHARMAC undertake a comprehensive review of the current PSO list, and that PHARMAC could consider adding or removing some pharmaceuticals.

5.11. The Subcommittee considered that it would be reasonable for PHARMAC to consider removing ciprofloxacin and trimethoprim from the PSO list. Members considered it unnecessary to have them on the list as nitrofurantoin is already available, which is the first-line agent for the treatment of uncomplicated urinary tract infection. Members considered that timely use of ciprofloxacin may help to prevent hospitalisation for management of pyelonephritis and considered that this would be important for patients living in rural setting. However, Members noted that the PSO list is predominantly used in urban setting, thus the inclusion of ciprofloxacin on the PSO list is less relevant.

5.12. The Subcommittee considered that it would be reasonable for PHARMAC to consider adding chloramphenicol eye drops or ointment, hydrogen peroxide cream 1% and miconazole cream 2% to the PSO list.

5.13. The Subcommittee considered that flucloxacillin granules for oral liquid is not palatable for children and that cefaclor granules for oral liquid 125 mg per 5 ml may be more suitable for inclusion on the PSO list.

5.14. The Subcommittee noted that erythromycin is on the PSO list, however, it is poorly tolerated with about one third of patients discontinuing treatment due to gastrointestinal issues. The Subcommittee considered that roxithromycin would be more appropriate to include on the PSO list than erythromycin due to greater tolerability of roxithromycin. Members noted that the treatment of rheumatic fever in accordance with guidelines for the treatment of strep throat requires one of these agents and considered that availability on the PSO list offers equity benefits.

Pre-exposure prophylaxis (PrEP)

5.15. The Subcommittee noted that in November 2017, the Anti-Infective Subcommittee reviewed an application from the New Zealand Aids Foundation which sought to widen funding of tenofovir disoproxil with emtricitabine (TD/FTC) for HIV pre-exposure prophylaxis (PrEP). At that time, the Subcommittee recommended widening the listing TD/FTC for PrEP with a high priority. The Subcommittee noted that, in February 2018, PHARMAC announced a decision to widen funded access to TD/FTC for PrEP from March 2018.

5.16. The Subcommittee noted that in May 2019, the Anti-Infective Subcommittee recommended additional changes to the PrEP Special Authority criteria to widen the prescriber access to initial applications and to cover the testing and considerations required for community initiations of the treatment. The Subcommittee noted that PHARMAC implemented the recommended changes in October 2019.

5.17. The Subcommittee noted that PHARMAC had received a number of correspondences from the Canterbury Syphilis Working Group (CSWG) requesting review of the criteria for TD/FTC for PrEP. The Subcommittee suggested changes to the current access criteria wording, and also noted the views of the CSWG including the following:

- The current criteria may disincentivise condom use, potentially encouraging the spread of other sexually transmitted infections (e.g. syphilis); and

- Noting the increased prevalence of STIs nationally, and particularly among men who have sex with men, condom use should be encouraged and amending the criteria to align with the Australasian Society of Sexual Health Medicine (ASHM) guidelines for PrEP would do this.

5.18. The Subcommittee noted that PHARMAC had received an application from Body Positive Inc. to broaden the prescriber access for TD/FTC for PrEP, to include an evidence-based dosing regimen for TD/FTC for PrEP and to remove the access criteria for TD/FTC for PrEP altogether as they consider that current access depends on patient being willing to disclose their sexual behaviour and methamphetamine use to the GPs.

5.19. The Subcommittee noted that PHARMAC had received correspondence from a General Practitioner who considered that the criteria for TD/FTC for PrEP should be reviewed because the criteria included invasive questions that are associated with a lot of stigma and which present barriers to men accessing the treatment.

5.20. The Subcommittee noted that PHARMAC had received correspondence from the New Zealand AIDS Foundation (NZAF) and Family Planning New Zealand (FPNZ) as part of the consultation process for the proposal relating to Schedule changes made in response to COVID-19, and that this correspondence requested PHARMAC to review the current criteria for TD/FTC for PrEP due to the following views of the NZAF and FPNZ:

- For patients with no recent test results for HIV, STI and renal function, PrEP should be prescribed on the same day as laboratory tests are ordered, with patients advised to only fill their prescription once informed it is safe to do so; and

- An undiagnosed bacterial STI does not constitute a contraindication to PrEP use; such cases could be followed up after treatment is initiated; and

- Barriers to accessing PrEP include cost, time, and the necessity to discuss intimate details of sexual practices with clinicians. The correspondence noted that studies show that half of gay and bisexual men in New Zealand are not open with their clinicians, and that 34% of men who have sex with men who would like to use PrEP stated that discussing the issue with their General Practitioner was a barrier.

5.21. In regard to the laboratory testing criteria for TD/FTC for PrEP, the Subcommittee considered that the requirement for recent results, particularly HIV serology, to be known at the time of prescribing is important to ensure appropriate treatment and management (e.g. if HIV positivity is reported, provisions would be made to protect the person and community), and considered that the funding criteria should not be amended in this regard at this time.

5.22. In regard to the criteria for TD/FTC for PrEP including invasive questions about sexual practices and drug use that may present a barrier to access, the Subcommittee acknowledged that the questions were confronting and that many people would not want to answer them. The Subcommittee noted that the criteria were based on international guidelines intended to indicate whether sexualised drug use (“chem sex”) was likely to occur, as this would target treatment to a patient group who are at risk of contracting HIV. The Subcommittee considered that it was reasonable to amend the question regarding methamphetamine use in the criteria.

5.23. The Subcommittee considered that the timeframe for recent STI in the Special Authority criteria for TD/FTC for PrEP should be widened to one year to allow for changes in sexual habits as a result of the recent COVID-19 lockdown and to ensure that potential concerns about disclosing lockdown non-adherence would not prevent access to treatment. The Subcommittee noted that this timeframe would align with the Scottish guidelines.

5.24. The Subcommittee noted that, if access to TD/FTC for PrEP were to be signifcantly widened (e.g. through removal of all at-risk criteria under point 6) it would require substantial and timely health system support including much greater GP involvement in providing PrEP prescriptions than has occurred to date. The Subcommittee considered that such widened criteria would result in a considerable increase in the

current estimate of eligible people (i.e. approximately 18% or 5800) of higher-risk HIV negative MSM, becoming potentially eligible for TD/FTC for PrEP. Overall, the Subcommittee did not support significantly widening access to TD/FTC for PrEP in this way at this time but considered that this could be reconsidered in future.

5.25. The Subcommittee considered that the prescriber types for the current Special Authority for TD/FTC for PrEP were appropriate and did not require amendment.

5.26. The Subcommittee considered that the Special Authority criteria for TD/FTC for PrEP should be amended as follows (additions shown in **bold**, deletions shown in ~~strikethrough~~):

Special Authority for Subsidy
Initial application from any relevant practitioner. Approvals valid for 3 months for applications meeting the following criteria:
All of the following:

1. Applicant has an up to date knowledge of the safety issues and is competent to prescribe pre-exposure prophylaxis (refer to local health pathways or https://ashm.org.au/HIV/PrEP/ for training materials); and
2. Patient has undergone testing for HIV, syphilis and Hep B if not immune in the previous two weeks; and
4. Patient has had renal function testing (creatinine, phosphate and urine protein/creatinine ratio) within the last 3 months and is not contraindicated for treatment; and
3. Patient has received advice regarding the reduction of risk of HIV and sexually transmitted infections and how to reduce those risks (e.g. Such as the importance of condom use); and
4. Patient has tested HIV negative and is not at risk of HIV seroconversion; and
5. Either:
   6.1 All of the following:
      6.1.1 Patient is male or transgender; and
      6.1.2 Patient has sex with men; and
      ~~6.1.3 Patient is likely to have multiple episodes of condomless anal intercourse in the next 3 months; and~~
      6.1.4 Any of the following:
         6.1.4.1 Patient has had at least one episode of condomless receptive anal intercourse with one or more casual male partners in the last 3 months; or
         6.1.4.2 A diagnosis of rectal chlamydia, rectal gonorrhoea, or infectious syphilis within the last **12** ~~3~~ months; or
         6.1.4.3 Patient has **experienced sexualised drug use ~~("chem sex")~~** ~~used methamphetamine~~ in the last three months; or
         6.1.4.4 Patient is likely to have more than one episode ~~multiple episodes~~ **of condomless anal intercourse in the next 3 months;** ~~and~~ **or**
   6.2 All of the following:
      6.2.1 Patient has a regular partner who has HIV infection; and
      6.2.2 Partner is either not on treatment or has a detectable viral load; and
      ~~6.2.3 Condoms have not been consistently used.~~

Renewal from any relevant practitioner. Approvals valid for 3 months for applications meeting the following criteria:
All of the following:

1. Applicant has an up to date knowledge of the safety issues and is competent to prescribe pre-exposure prophylaxis (refer to local health pathways or https://ashm.org.au/HIV/PrEP/ for training materials); and
2. Patient has undergone testing for HIV, syphilis and Hep B if not immune in the previous two weeks; and
3. Patient has had renal function testing (creatinine, phosphate and urine protein/creatinine ratio) within the last 12 months and is not contraindicated for treatment; and
4. Patient has received advice regarding the reduction of risk of HIV and sexually transmitted infections and how to reduce those risks **(e.g. Such as the importance of condom use);** and
5. Patient has tested HIV negative and is not at risk of HIV seroconversion; and
6. Either:
   6.1 All of the following:
   6.1.1 Patient is male or transgender; and
   6.1.2 Patient has sex with men; and

~~6.1.3 Patient is likely to have multiple episodes of condomless anal intercourse in the next 3 months; and~~
6.1.4 Any of the following:
6.1.4.1 Patient has had at least one episode of condomless receptive anal intercourse with one or more casual male partners in the last 3 months; or
6.1.4.2 A diagnosis of rectal chlamydia, rectal gonorrhoea, or infectious syphilis within the last **12** ~~3~~ months; or
6.1.4.3 Patient has **experienced sexualised drug use** ~~**("chem sex")** used methamphetamine~~ in the last three months; or
6.1.4.4 Patient is likely to have more than one episode ~~multiple episodes~~ **of condomless anal intercourse in the next 3 months;** ~~and~~ **or**
6.2 All of the following:
6.2.1 Patient has a regular partner who has HIV infection; and
6.2.2 Partner is either not on treatment or has a detectable viral load; and
~~6.2.3 Condoms have not been consistently used.~~

Non-occupational post-exposure prophylaxis (nPEP)

5.27. The Subcommittee noted that in May 2019, the Anti-Infective Subcommittee reviewed an application from the New Zealand Aids Foundation (NZAF) which sought to expand eligibility criteria for nPEP to include receptive anal sex with a person of unknown HIV serostatus, and to amend the prescriber types to include sexual health physicians, nurse practitioners in a sexual health clinic and GPs who have undergone accredited PEP and PrEP training. At that time, the Subcommittee recommended that the Special Authority criteria for nPEP be amended and as described in the May 2019 meeting record.

5.28. The Subcommittee noted that PHARMAC had received correspondence from the New Zealand Sexual Health Society (NZSHS), which supported the NZAF submission considered by the Subcommittee in May 2019. The NZSHS correspondence suggested that prescriber types for PEP should be expanded to include General Practitioners and nurse practitioners as requiring named specialist prescribers could be a barrier to timely treatment. NZSHS also supported widening of access to HIV negative individuals who are at elevated risk of HIV exposure.

5.29. The Subcommittee noted that PHARMAC had received correspondence from a General Practitioner who raised concerns around access to PEP (including privacy, equity and training considerations) and requested PHARMAC to review the current criteria.

5.30. The Subcommittee considered that the suggestions and issues raised in these items of correspondence were considered and addressed by the Subcommittee in May 2019. The Subcommittee considered that no new concerns or information were raised.

Ivermectin

5.31. The Subcommittee noted that PHARMAC had received correspondence from a public health physician requesting the current Special Authority criteria for ivermectin be removed to enable access by General Practitioners for the treatment of scabies infestation. The Subcommittee noted that the rationale for this request was as follows:

- Scabies can lead conditions such as bacterial skin infection, post-streptococcal glomerulonephritis, and possibly acute rheumatic fever, which are more common in the Pacific and Māori population; and

- The requestor indicates that better control of scabies may reduce burden of acute rheumatic fever in NZ; and

- Although increasingly and internationally accepted evidence supports grp A strep skin infection precede rheumatic fever, there is not clear accepted correlation between scabies and rheumatic fever; and

- Having a better control of scabies with ivermectin may reduce the burden of acute rheumatic fever in New Zealand; and

- Topical application of permethrin leads to resistance and adherence issues especially in large Pacific families; and

- The requestor indicates ivermectin would be likely to help with the compliance issues, especially in large households since it is an oral medication; and

- Large studies carried out in Pacific Island nations indicated that treatment with ivermectin is conclusively superior to permethrin; and

- The clinician noted this is a likely cause of health inequity.

5.32. The Subcommittee noted that two presentations of permethrin (cream 5% and lotion 5%) are both listed without any restrictions. The Subcommittee also noted that the ivermectin 3 mg tablet is available on PSO for institutional use, and on BSO provided the BSO includes a valid Special Authority for a patient of the institution. The Special Authority criteria restricts the funding of ivermectin to be prescribed only for complicated and severe cases of scabies, or for when the patient is unable to comply with permethrin or they have failed topical therapy.

5.33. The Subcommittee considered that permethrin is effective and that there is no documented resistance to permethrin. However, the Subcommittee acknowledged that topical treatment is not practical in all cases.

5.34. The Subcommittee considered that scabies is not an increasing issue in New Zealand as it is being seen less frequently in school programmes, although a greater proportion of cases may be seen by General Practitioners. The Subcommittee noted that the main issue for treatment of scabies is the rate of relapse and considered that skin programmes are more effective than treatment interventions used broadly. Members considered that there is insufficient evidence to suggest direct association between scabies and rheumatic fever.

5.35. Overall, the Subcommittee considered that the correspondence received did not provide sufficient information to support removal of the Special Authority criteria for ivermectin and could be considered that this could be reviewed in future if relevant evidence were provided for lack of effectiveness of permethrin or increased need for ivermectin for the treatment of scabies.

Cefazolin

5.36. The Subcommittee noted that PHARMAC received a funding application from a clinical microbiologist for the funding of a larger size of cefazolin vial for injection (2 g) for use in prophylaxis of surgical site infection. The Subcommittee noted that cefazolin 500 mg vials and 1 g vials for injection are currently funded.

5.37. The Subcommittee noted that the applicant's request for a larger vial size is primarily a suitability issue as the applicant considers that funding 2 g vials would reduce wastage associated with surgical prophylaxis of patients who weigh >80 kg (approximately 60%

of patients) and that this would save time in operating rooms and on post-op wards following cardiac and orthopaedic surgery.

5.38. The Subcommittee noted that the application was accompanied by a letter from the Health Quality and Safety Commission's Surgical Site Infection Improvement Programme which outlines that listing the 2 g vial would reduce the risk of contamination, time in dose preparation and waste in consumables and diluent used.

5.39. The Subcommittee noted that the applicant provided a clinical research report titled "Surgical site infection rate is higher following hip and knee arthroplasty when cefazolin is underdosed" which recommends a higher cefazolin dose than standard of 1 g for patients over 80 kg, or under 3 g for patients over 120 kg. The Subcommittee noted that the applicant considers adherence to 2 g dosing would improve with funded use of 2 g vials.

5.40. The Subcommittee considered that there was no unmet health need in this patient population and that the potential benefits were predominantly related to suitability. The Subcommittee considered that it would be reasonable to list the 2 g vial if cost-neutral relative to the currently funded 1 g vial.

5.41. The Subcommittee noted that all three strengths of cefazolin (500 mg, 1 g, and 2 g vials) were included in the 2019/2020 Invitation-to-tender and PHARMAC resolved to award tenders to 500 mg and 1 g presentations only, and to decline the bid for 2 g presentation in June 2020.

6. Rifampicin/Isoniazid/Pyrazinamide/Ethambutol- fixed dose combinations for tuberculosis -1

Application

6.1. The Subcommittee reviewed the clinician application for a four-drug fixed dose combination (FDC) tablet containing rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg and ethambutol hydrochloride 275 mg (Rimstar, Voractiv; from Sandoz UK) for the treatment of tuberculosis according to World Health Organization (WHO) and New Zealand treatment guidelines.

6.2. The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

6.3. The Subcommittee recommended Subcommittee **recommended** that the application for the rifampicin/isoniazid/pyrazinamide/ethambutol fixed dose combination (FDC) tablet be funded with a **high priority**, within the context of anti-infective treatments.

6.4. In making this recommendation, the Subcommittee considered:

- The likely reduction in pill burden and improved suitability of a fixed-dose combination tablet;
- Potentially improved adherence and avoidance of selective non-adherence associated with currently available formulations;
- The health need of people and wider society in New Zealand due to tuberculosis (an ongoing public health issue);
- The possibility of unquantified but potentially large cost savings with a fixed dose combination tablet; and
- That the risks and challenges associated with dosing using a fixed-dose combination tablet were manageable provided individual tablets remain funded.

Discussion

6.5. The Subcommittee noted that tuberculosis is a bacterial infection caused by *Mycobacterium tuberculosis* and is a major cause of morbidity and mortality worldwide. The Subcommittee noted that the World Health Organization (WHO) estimates about ten million people are diagnosed with tuberculosis annually and over half of the TB cases occur in South East Asia and the Western Pacific.

6.6. The Subcommittee noted that tuberculosis is a notifiable disease and that notification rates in New Zealand between 2011 and 2015 were between 6.2-7.0 per 100,000 in the population (Ministry of Health, 2019), equivalent to about 314 people per year in New Zealand with tuberculosis. The Subcommittee noted that the vast majority of patients with tuberculosis in New Zealand were born outside of New Zealand (Ministry of Health, 2019) and that between 2012 and 2016, the percentages of cases were higher for areas with higher deprivation.

6.7. The Subcommittee noted that the Guidelines for Tuberculosis Control in New Zealand (2019. Wellington: Ministry of Health) state that the initial treatment of drug-sensitive tuberculosis in adults and children over 8 years of age usually includes two months of intensive treatment (bactericidal phase), followed by four months of treatment in a continuation or sterilisation phase. The Subcommittee noted that tuberculosis treatment would most often be commenced in a hospital setting rather than in the community.

6.8. The Committee noted that first-line funded treatment of tuberculosis consists of four medicines, either administered as individual tablets or as a two-drug combination tablet plus other individual tablets. The Subcommittee noted the applicant considers that daily dosing with currently funded treatments for tuberculosis would consist of isoniazid/rifampicin (two 150/300 mg tablets combining both medicines), pyrazinamide (four 500 mg tablets) and ethambutol (two 400 mg tablets) which is equivalent to a total daily intake of 600 mg rifampicin, 300 mg isoniazid, 2,000 mg pyrazinamide and 1,000 mg ethambutol (based on a 70 kg patient), achieved with 11 tablets per day.

6.9. The Committee considered that tuberculosis requires a long duration of treatment, that patients with tuberculosis have a high health need, and noted that there is a public health risk for patients with active tuberculosis and that this therefore conveys a health need onto others.

6.10. The Subcommittee noted that current funded therapy requires a high number of tablets daily and considered that this can contribute to poor adherence and confusion, or

patients may choose to be selectively non-adherent e.g. by not taking a particular medication. The Subcommittee considered that these challenges can lead to development of resistant tuberculosis, resulting in prolonged treatment of approximately six to nine months with high-cost second-line regimens.

6.11. The Subcommittee noted that the fixed-dose combination (FDC) tablet contains the four first-line medicines used for the treatment of tuberculosis; rifampicin 150mg + isoniazid 75mg + pyrazinamide 400mg + ethambutol 275mg for use in the bactericidal (intensive) phase of treatment, with dosing according to bodyweight category (i.e. 30-39kg: two tablets daily; 40-54kg: three tablets; 55-70kg: four tablets; >70kg: five tablets). The Subcommittee noted the applicant's proposed dosing of five tablets daily of rifampicin/isoniazid/pyrazinamide/ethambutol 150 mg/75 mg/400 mg/275 mg is equivalent to a total daily intake of 750 mg rifampicin, 375 mg isoniazid, 2,000 mg pyrazinamide and 1,375 mg ethambutol based on a 70 kg patient.

6.12. The Subcommittee noted that no fixed-dose combination rifampicin/isoniazid/pyrazinamide/ethambutol tablet has been approved by Medsafe nor has an application for one been submitted to Medsafe. The Subcommittee noted that all individual agents are currently approved by Medsafe in New Zealand except ethambutol which is currently supplied under Section 29 of the Medicines Act 1981.

6.13. The Subcommittee noted that the World Health Organization Model List of Essential Medicines, 21st List (Geneva: World Health Organization; 2019) recommends the use of fixed-dose combinations including the 275/75/400/150 mg fixed-dose combination tablet for tuberculosis.

6.14. The Subcommittee noted that the Guidelines for Tuberculosis Control in New Zealand consider the advantages of fixed-dose combinations are the reduced risk of resistance developing, reduction in medication errors and fewer prescription items. The Subcommittee noted that the recommended dosages of each of the four first-line agents is presented as both a maximum dose per kilogram, and as a maximum dose per day. Members considered that reduced bioavailability of some medicines (e.g. rifampicin) was not a concern with the fixed-dose combination tablet.

6.15. The Subcommittee considered that weight-based dosing (i.e. mg per kg, presented as a value range) was challenging in tuberculosis treatment and noted that the New Zealand tuberculosis guidelines specify weight-based doses that may be difficult to achieve precisely in some patients with use of fixed-dose combination tablets alone.

6.16. The Subcommittee considered that the dosing of the fixed-dose combination according to bodyweight category appeared consistent with the expected bodyweight of patients with tuberculosis in New Zealand. However, the Subcommittee considered that it could under-dose some patients with low weight or whose weight is near the range limits at higher doses compared to currently funded individual drug regimens. Members considered that dosing with four tablets per day may be more suitable for a 70 kg patient than five tablets, although this would result in a lower daily dose of pyrazinamide than the funded individual drug regimen.

6.17. Members noted a systematic review and meta-analysis of fixed dose combination tuberculosis therapy that states that fixed-dose combination formulations simplify tuberculosis treatment and are associated with a trend towards reduction in treatment failure or relapse (Albanna et al. Eur Resp J. 2013;42:721-32). The authors report a statistically insignificant difference in drug resistance and adverse drug reactions and a clinically unimportant difference in culture conversion after two months of treatment. Members noted the authors also state that fixed-dose combinations are not superior to

individual tablets and acknowledge that none of the included studies identified improved adherence with the fixed-dose combination compared to separate formulations.

6.18. The Subcommittee noted a Cochrane review of fixed-dose combinations of drugs versus single-drug formulations for treating pulmonary tuberculosis, from 13 randomised controlled trials that reported results between 1987 and 2015 that included 5,824 patients treated for newly diagnosed pulmonary tuberculosis in countries with high tuberculosis prevalence (Gallardo et al. Cochrane Database Syst Rev. 2016;2016(5):CD009913). The Subcommittee noted that the authors reported that there was similar efficacy with fixed-dose combination compared to single-drug formulations for the treatment of newly diagnosed tuberculosis based on moderate quality evidence.

6.19. The Subcommittee also noted the following evidence which primarily consisted of applicant-identified evidence regarding fixed-dose combinations and/or the treatment of tuberculosis, in addition to other relevant evidence identified by PHARMAC:

- Lienhardt et al. JAMA. 2011;305:1415-23 (The Study C Trial: a parallel-group, open-label, non-inferiority, randomised controlled trial; N = 1,585)
- Bartacek et al. Int J Tuberc Lung Dis. 2009;13:760-6 (randomised, multi-centre, open-label study; N = 1,159)
- Aseffa et al. PLoS One. 2016;11:e0157434 (single-blind, randomised clinical trial; N = 1,000)
- Wu et al. Clinics. 2015;70:429-34 (prospective, open-label, randomised controlled study; N = 161)
- Bangalore et al. Am J Med. 2007;120:713-9 (systematic review and meta-analysis including patients with tuberculosis; N = 20,242)
- Lima et al. Braz J Microbiol. 2017;48:198-207 (systematic review and meta-analysis; N = 3,502)
- Krasniqi et al. Tuberc Res Treat. 2017;2017:4850324 (descriptive study; N = 324)
- Mekonnen et al. BMC Res Notes. 2018;11:691 (cross-sectional study; N = 314)
- Farrell et al. Can Pharm J (Ott). 2013;146:262-9 (case study; N = 1)
- Cohen et al. J Hosp Med. 2012;7:470-5 (randomised controlled trial of patients hospitalized on cardiology/general medical/geriatric services)
- Kadhiravan T. Indian J Chest Dis Allied Sci. 2013;55:9-10 (editorial)
- The Economic Cost of Non-adherence to TB Medicines Resulting from Stock-outs and Loss to Follow-up in Kenya (2016) (report)

6.20. Overall, the Subcommittee noted that the evidence for fixed-dose combinations for tuberculosis indicated that there was no difference in treatment outcomes compared with individual tablets. There was insufficient robust data to show an improved adherence with the fixed-dose combination, compared with individual tablets, but a decline in adherence would be improbable.

6.21. The Subcommittee considered that the main benefit of the fixed-dose combination for tuberculosis appeared to be the reduced pill burden which could increase patient

adherence to treatment. The Subcommittee considered that this would likely lead to reduced patient confusion around dosing and reduced selective non-adherence. The Subcommittee considered that the fixed-dose combination could also offered greater convenience and simplicity than the funded individual tablets.

6.22. The Subcommittee noted that informal discussion with treating clinicians in New Zealand had identified strong support for the funded use of this particular fixed-dose combination and that the clinicians considered that it would improve patient care and adherence, and would reduce prescribing risks.

6.23. The Subcommittee considered that, if the fixed-dose combination were to be funded for the treatment of tuberculosis, it would be important for all individual tablets to remain funded to manage toxicity and rechallenge, to facilitate optimal dosing (noting variation in patient weight including low weights and weights near the range limits at higher doses) and to allow for flexibility in patient management (e.g. for patients receiving treatment with complicated regimens).

6.24. The Subcommittee considered that the fixed-dose combination could be cost-effective or potentially cost-saving, depending on price. The Subcommittee considered that no funding criteria would be required to restrict access because the fixed-dose combination would only be used for the treatment of tuberculosis, and because patient and clinician preferences including assessment of dosage calculations and options would determine whether to use fixed-dose combinations or individual medicines.

6.25. Overall, the Subcommittee considered that, whilst noting the lack of robust evidence demonstrating improvements in adherence and outcomes with the fixed-dose combination, from their expert perspective (or from a treating clinician perspective) the potential benefits of the fixed-dose combination (i.e. reduced pill burden, potential for improved adherence, improved suitability, and the possibility of cost savings) outweighed the manageable risks associated with potentially underdosing patients if the fixed-dose combination were used alone for all bodyweights, and needing to access individual tablets in cases of toxicity.

7. Letermovir- Cytomegalovirus infection prophylaxis (stem cell transplant patients)

Application

7.1. The Subcommittee reviewed the application for letermovir for cytomegalovirus infection prophylaxis in allogenic haematopoietic stem cell transplant patients.

7.2. The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

7.3. The Subcommittee **recommended** that letermovir for cytomegalovirus infection prophylaxis in haematopoietic stem cell transplant patients be listed with a **low priority** within the context of treatments for infections, subject to the following Special Authority criteria:

Special Authority for Subsidy
Initial application only from a haematologist or infectious disease specialist; approvals valid for four months for applications meeting the following criteria:
All of the following:

1 Patient must have undergone an allogeneic haematopoietic stem cell transplant; and
2 The patient must have confirmed presence of cytomegalovirus-specific antibodies; and
3 Treatment must commence within 28 days of an allogeneic haematopoietic stem cell transplant; and
4 Maximum treatment duration of one hundred days.

7.4. The Subcommittee made this recommendation due to:

7.4.1. The high health need of patients who develop cytomegalovirus disease following allogenic haematopoietic stem cell transplant;

7.4.2. Evidence that demonstrates that letermovir reduces cytomegalovirus infection, which has the potential decrease the use of pre-emptive therapy (PET);

7.4.3. The lack of evidence of significant difference in mortality between letermovir and placebo in this setting.

Discussion

7.5. The Subcommittee noted that following initial infection, cytomegalovirus establishes a life-long latent infection in the host and is usually asymptomatic. The Subcommittee noted that patients who have undergone allogeneic haematopoietic stem cell transplant are heavily immunocompromised, which can result in cytomegalovirus reactivation (in cytomegalovirus seropositive patients) or cytomegalovirus arising de novo (if cytomegalovirus seronegative), and either way may lead to severe cytomegalovirus disease.

7.6. The Subcommittee noted that the highest risk for cytomegalovirus infection and cytomegalovirus disease has been reported for haematopoietic stem cells transplant patients who are cytomegalovirus seropositive, regardless of donor serostatus (Styczynski. Infect Dis Ther. 2018;7:1-16). The Subcommittee noted that the risk of developing cytomegalovirus infection is the greatest in the first 100 days post-transplant (Bhat et al. World J Transplant. 2015;5:287-91).

7.7. The Subcommittee noted that cytomegalovirus reactivation has been reported in up to 60-80% of patients with positive cytomegalovirus serology who have undergone allogeneic haematopoietic stem cell transplants, with approximately one-third of these patients going on to develop symptomatic cytomegalovirus disease (Pollack et al. Biol Blood Marrow Transplant. 2011;17:664-73). The Subcommittee noted that cytomegalovirus disease has direct effects on various systems, which can result in end-organ disease, most commonly manifesting as pneumonia and gastrointestinal disease (Azevedo et al. Clinics. 2015;70:515-23). The Subcommittee noted that cytomegalovirus disease may also have indirect but other severe effects, such as increased incidence of Graft vs host disease (GvHD) and increased risk of serious bacterial and fungal infections, mediated by the pro-inflammatory and immunosuppressive properties of cytomegalovirus (Helou & Razonable. Infec Drug Resist. 2019;12:1481-91).

7.8. The Subcommittee noted that the development of cytomegalovirus viraemia is associated with poorer survival outcomes following allogeneic haematopoietic stem cell transplant, and that for cytomegalovirus seropositive patients any level of cytomegalovirus viraemia, including asymptomatic, low level infection, has been associated with an increased risk of overall mortality and morbidity (Green et al. Lancet Haematol. 2016;3:e119-27). The Subcommittee noted that lung infiltration of cytomegalovirus carries a 50% mortality.

7.9. The Subcommittee considered that currently patients who have undergone haematopoietic stem cell transplant have their viral load monitored weekly, and if evidence of viral replication is detected, a pre-emptive therapy (PET) approach is taken using either intravenous ganciclovir or oral valganciclovir. The Subcommittee noted that foscarnet is available as second-line PET for patients ineligible for, intolerant or resistant to ganciclovir/ valganciclovir.

7.10. The Subcommittee noted that in 2017, 104 allogeneic haematopoietic stem cell transplants were performed in New Zealand, and 86% of these patients were aged over 15 years (ABMTRR. 2018). The Subcommittee considered that the haematopoietic stem cell transplant population appears to be relatively consistent over time.

7.11. The Subcommittee noted that a study of cytomegalovirus seroprevalence of New Zealand blood donors indicated cytomegalovirus seropositivity increases with age, and that 93.3% of Pacific Islander donors, 80.4% of Māori donors, 77.6% of Asian donors and 54.9% of Caucasian donors were cytomegalovirus seropositive (Badami et al. Epidemiol Infect. 2009;137:1776-80).

7.12. The Subcommittee noted that letermovir inhibits the cytomegalovirus DNA terminase complex, required for viral replication, and in turn affects the formation of proper unit length genomes and interferes with virion maturation.

7.13. The Subcommittee noted that the recommended dose of letermovir is 240 mg once daily when used concurrently with ciclosporin or 480 mg once daily if not used with ciclosporin.

7.14. The Subcommittee noted the results of the P001 phase III, double-blind, placebo-controlled randomised trial investigating letermovir compared with placebo as prophylaxis for patients ≥18 years undergoing allogeneic haematopoietic stem cell transplant who were cytomegalovirus-seropositive and had an undetectable level of cytomegalovirus DNA (Marty et al. N Engl J Med. 2017. 21;377:2433-44). The Subcommittee noted that clinically significant cytomegalovirus infection through week 24 was reported in 37.5% of the letermovir group compared with 60.6% placebo (CMV risk stratum-adjusted absolute difference -23.5%, 95% confidence interval (CI) -32.5 to -14.6, p<0.001). The Committee noted that at week 48, there was no statistically significant difference in all-cause mortality between groups, 20.9% letermovir compared with 25.5% placebo (p=0.12). The Subcommittee noted that there were no statistically significant differences in adverse events reported. The Subcommittee considered that the trial was well designed and demonstrated a good comparison of letermovir to placebo.

7.15. The Subcommittee noted the results of a post-hoc analysis of the P001 trial that investigated the effect of letermovir on all-cause mortality in patients (Ljungman et al. Clin Infect. Dis. 2020;70:1525-33). The Subcommittee noted the hazard ratio (HR) for all-cause mortality at week 24 post-transplant for letermovir compared to placebo as 0.58 (95% CI: 0.35-0.98; p=0.04), however at week 48, there was no statistically significant difference observed (HR 0.74, 95% CI: 0.49–1.11; p=0.14). The Subcommittee noted that the incidence of all-cause mortality through week 48 post-haematopoietic stem cell transplant in the letermovir group was similar in patients with or without clinically significant cytomegalovirus infection (15.8% vs 19.4%; p=0.71). The Subcommittee noted that for patients who developed clinically significant cytomegalovirus infection, the HR for all-cause mortality was 0.45 (95% confidence interval, 0.21–1.00; p=0.05) at week 48 for letermovir compared with placebo.

7.16. The Subcommittee noted the results of a dose-determining study (Chemaly et al. N Eng J Med. 2014;370:1781-9). The Subcommittee noted that the incidence of prophylaxis failure was 29% for the 240 mg letermovir group compared with 64% for the placebo group (p=0.007). The Subcommittee noted that this dose had the lowest prophylaxis failure out of all doses investigated.

7.17. The Subcommittee noted that letermovir is not registered for use in people under 18 years of age and there is a lack for data of letermovir use in this population. The Subcommittee considered that haematopoietic stem cell transplants are protocolised and if letermovir were to be funded and incorporated into standardised protocol, it is likely that eligible patients under 18 years may also receive letermovir in this setting. The Subcommittee considered that there was little clinical basis for any Special Authority restrictions for letermovir to restrict by age.

7.18. The Subcommittee noted that currently patients do not routinely receive antiviral CMV prophylaxis following allogeneic haematopoietic stem cell transplant in New Zealand, and therefore the comparator would be placebo.

7.19. The Subcommittee considered that if letermovir were funded and incorporated into allogenic haematopoietic stem cell transplant protocol, uptake would be 95-100%, with only patients contraindicated not being offered and consenting to receive letermovir.

7.20. The Subcommittee considered that PET has associated toxicities, and any reduction in PET use would be of benefit both clinically and financially. The Subcommittee considered that the supplier's PET cost-estimates appeared to be outdated.

7.21. The Subcommittee noted that ciclosporin is often used post-transplant to prevent GvHD and considered that the supplier's estimate that 95% of patients would be prescribed ciclosporin and thus receive a lower dose of 240 mg letermovir was reasonable.

7.22. The Subcommittee noted letermovir is available as both oral and injection for infusion formulations and considered the assumption that 95% of patients would use the oral formulation was reasonable.

8. Bictegravir 50mg/Emtrictabine 200mg/Tenofovir alafenamide 25mg (BIKTARVY) for Treatment of HIV

Application

8.1. The committee reviewed the application from Gilead Sciences (NZ) for Bictegravir 50 mg/Emtricitabine 200 mg/Tenofovir alafenamide 25 mg (Biktarvy) in the treatment of HIV.

8.2. The committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

8.3. The committee **recommended** that Bictegravir 50 mg/Emtricitabine 200 mg/Tenofovir alafenamide 25 mg (Biktarvy) be listed as **cost neutral** to the weighted price of all currently funded HIV treatments, within the context of treatments for infections.

8.4. The Subcommittee made this recommendation because:

8.4.1. There is no unmet health need for HIV patients in New Zealand as currently funded HIV medications are effective and readily available.

8.4.2. Bictegravir/emtricitabine/tenofovir alafenamide has not demonstrated any superior efficacy compared to other currently funded HIV medications,

8.4.3. Bictegravir/emtricitabine/tenofovir alafenamide is likely to be preferred by patients and prescribers due to smaller tablet size compared to other treatments, as well as being a single tablet regimen, which may well have a large cost implication to the health system if it were to be funded.

8.4.4. Single tablet regimens such as bictegravir/emtricitabine/tenofovir alafenamide have not demonstrated any proven improvement of adherence to treatment compared to once daily multiple tablet regimens.

Discussion

8.5. The Subcommittee noted that there are approximately 3,500 people in New Zealand living with HIV, and that the majority of patients have well-controlled viral suppression with currently funded treatments. The Subcommittee noted that, Asian and Sub-Saharan African people have a higher incidence of HIV compared with other populations in New Zealand.

8.6. The Subcommittee considered that there are no issues with access or availability of effective antiretrovirals to treat HIV in New Zealand, and that there is not an unmet health need for this population currently.

8.7. The Subcommittee noted that bictegravir/emtricitabine/tenofovir alafenamide is a combination antiretroviral containing two nucleoside/nucleotide reverse transcriptase inhibitors, emtricitabine and tenofovir alafenamide, and the novel un-boosted integrase strand transfer inhibitor, bictegravir. The Subcommittee noted that, as with most current HIV treatments, bictegravir/emtricitabine/tenofovir alafenamide requires once-daily dosing.

8.8. The Subcommittee noted that bictegravir/emtricitabine/tenofovir alafenamide is only 15 mm in length and is thinner than most other antiretroviral tablets. The Subcommittee noted that the tablet is close to a third of the volume of the efavirenz/emtricitabine/tenofovir disoproxil (Atripla) tablet which is currently the only funded single tablet regimen for the treatment of HIV. The Subcommittee considered that a smaller tablet size would be preferable to many patients.

8.9. The Subcommittee noted that bictegravir/emtricitabine/tenofovir alafenamide does not require pharmacokinetic boosting, has a high genetic barrier to resistance, and is suitable for patients with chronic hepatitis B coinfection. The Subcommittee noted that tenofovir alafenamide is not currently available in New Zealand; however, there are already tenofovir disoproxil-free treatments available for the small number of patients with tenofovir disoproxil associated renal toxicity. The Subcommittee noted that tenofovir alafenamide would be of benefit for patients with chronic hepatitis B with tenofovir disoproxil associated renal toxicity and that it could be of benefit for patients with proven osteoporosis who have limited treatment options with other standard antiretrovirals.

8.10. The Subcommittee noted the following trials:

8.10.1 Sax et al. Lancet. 2017;390:2073-2082: a phase III, double-blind, multicentre, placebo-controlled, randomised controlled non-inferiority trial (1490 trial) in which

treatment-naïve adult patients with HIV infection were randomised 1:1 to receive bictegravir/emtricitabine/tenofovir alafenamide (n=327) or dolutegravir/emtricitabine/tenofovir alafenamide (n=330). The Subcommittee noted that 89% of the bictegravir/emtricitabine/tenofovir alafenamide patients reached the primary endpoint (viral load < 50 copies/mL at week 48) compared with 93% of the dolutegravir/emtricitabine/tenofovir alafenamide patients (95% CI -7.9 to 1.0, p=0.12) demonstrating that bictegravir/emtricitabine/tenofovir alafenamide was non-inferior to dolutegravir/emtricitabine/tenofovir alafenamide, with no emergent antiretroviral resistance in either group.

8.10.2 Stellbrink et al. Lancet HIV. 2019; 6:e364-e372: The follow-on from the 1490 trial at 96 weeks. The Subcommittee noted that 84% of the bictegravir/emtricitabine/tenofovir alafenamide patients reached the primary endpoint (viral load < 50 copies/mL at week 96) compared with 86% of the dolutegravir/emtricitabine/tenofovir alafenamide patients (95% CI, -7.9 to 3.2) demonstrating that bictegravir/emtricitabine/tenofovir alafenamide was non-inferior to dolutegravir/emtricitabine/tenofovir alafenamide, with no emergent antiretroviral resistance in either group.

8.10.3 Gallant et al. Lancet. 2017;390(10107):2063-2072: a phase III, double-blind, multicentre, active-controlled, randomised controlled non-inferiority trial (1489 trial) in which treatment-naïve adult patients with HIV infection were randomised 1:1 to receive bictegravir/emtricitabine/tenofovir alafenamide (n=316) or co-formulated dolutegravir/abacavir/lamivudine (n=315). The Subcommittee noted that 94% of the bictegravir/emtricitabine/tenofovir alafenamide patients reached the primary endpoint (viral load < 50 copies/mL at week 48) compared with 93% of the dolutegravir/abacavir/lamivudine patients (95% CI -4.8 to 3.6, p=0.78) demonstrating that bictegravir/emtricitabine/tenofovir alafenamide was non-inferior to dolutegravir/abacavir/lamivudine, with no emergent antiretroviral resistance in either group.

8.10.4 Wohl et al. Lancet HIV. 2019; 6(6):e355-e363: The follow-on from the 1489 trial at 96 weeks.. The Subcommittee noted that 88% of the bictegravir/emtricitabine/tenofovir alafenamide patients reached the primary endpoint (viral load < 50 copies/mL at week 96) compared to 90% of the dolutegravir/abacavir/lamivudine patients (95% CI, -6.9 to 3.1) demonstrating that bictegravir/emtricitabine/tenofovir alafenamide was non-inferior to dolutegravir/abacavir/lamivudine, with no emergent antiretroviral resistance in either group.

8.10.5 Molina et al. Lancet HIV. 2018;5:e357-e365: a randomised, double-blind, multicentre, active controlled, non-inferiority, phase III trial (1844 trial) in which adults with HIV infection who were virologically suppressed (viral load < 50 copies/mL for ≥ 3 months) with treatment with dolutegravir/abacavir/lamivudine were randomised 1:1 to switch to bictegravir/emtricitabine/tenofovir alafenamide (n=282) or remain on current combination (n=281). The Subcommittee noted that 1% of the bictegravir/emtricitabine/tenofovir alafenamide patients reached the primary endpoint (≥ 50 copies/mL at week 48) compared with <1% of the dolutegravir/abacavir/lamivudine patients (95% CI -1.0 to 2.8, p=0.62) demonstrating that bictegravir/emtricitabine/tenofovir alafenamide was non-inferior to dolutegravir/abacavir/lamivudine, with no emergent antiretroviral resistance in either group.

8.10.6 Daar et al. Lancet HIV. 2018;5:e347-e356: a randomised, open-label, multicentre, active-controlled, non-inferiority, phase III trial (1887 trial) in which

adults with HIV infection who were virologically suppressed (viral load < 50 copies/mL for ≥ 6 months before screening) receiving either a boosted atazanavir or darunavir based combination (protease inhibitor) were randomised 1:1 to switch to bictegravir/emtricitabine/tenofovir alafenamide (n=290) or remain on current combination (n=287). The Subcommittee noted that 2% of the bictegravir/emtricitabine/tenofovir alafenamide patients reached the primary endpoint (≥ 50 copies/mL at week 48) compared with 2% of the protease inhibitor patients (95% CI -2.5 to 2.5) demonstrating that bictegravir/emtricitabine/tenofovir alafenamide was non-inferior to the protease inhibitors, with no emergent antiretroviral resistance in either group.

8.10.7 Wohl et al. Patient. 2018;11:561-573: secondary analysis of patient reported outcomes from the 1489 and 1844 trials. The Subcommittee noted that bothersome symptoms (ie fatigue, dizziness/light-headedness, nausea/vomiting, difficulty sleeping, loss of appetite, headaches, bloating/pain/gas, and changes in body composition) were reported by less patients who received bictegravir than those who received dolutegravir, and that four of the seven authors are employed by Gilead Sciences.

8.11. The Subcommittee noted preliminary unpublished evidence presented at the European AIDS Clinical Society Conference in 2019, comparing tenofovir alafenamide/emtricitabine/dolutegravir, tenofovir disoproxil/emtricitabine/dolutegravir and tenofovir disoproxil/emtricitabine/efavirenz. The Committee noted that the trial patients taking tenofovir alafenamide had a high chance of developing obesity, and that this population would be comparable to the New Zealand patient population. The Subcommittee considered that tenofovir alafenamide with an integrase inhibitor may result in significant rates of obesity and associated metabolic complications but noted that there is currently no peer-reviewed, published data to demonstrate this. The Subcommittee noted that the metabolic effects of tenofovir alafenamide also included an increase in high density lipoproteins across all studies and considered this to be concerning considering the long-term effects of this are unknown.

8.12. The Subcommittee considered the evidence provided was of high quality, although lacking in long-term follow-up. The Subcommittee considered that the evidence showed that bictegravir/emtricitabine/tenofovir alafenamide has potent antiviral activity and that it is non-inferior to currently available HIV antiretroviral treatments. The Subcommittee also noted that, compared to tenofovir disoproxil, tenofovir alafenamide results in a 90% reduction in plasma tenofovir exposure, thus reducing renal and bone exposure and toxicity. The Subcommittee considered that bictegravir is as good as dolutegravir, which is most commonly prescribed in the first line treatment of HIV in New Zealand.

8.13. The Subcommittee considered that, if bictegravir/emtricitabine/tenofovir alafenamide were to be funded, it would be preferred over boosted protease inhibitor-based regimens, dolutegravir/emtricitabine/tenofovir disoproxil, dolutegravir/abacavir/lamivudine, and efavirenz/emtricitabine/tenofovir disoproxil.

8.14. The Subcommittee considered that the combination of a single tablet regimen, a small tablet size, and tenofovir alafenamide availability will make bictegravir/emtricitabine/tenofovir alafenamide an attractive option for patients and health professionals. The Subcommittee considered that, if it were to be funded, there would be 50 to 75% uptake in the first 12-24 months, from the total HIV patient population in New Zealand. The Subcommittee considered that there may be an even greater uptake in patients currently on a boosted protease-inhibitor regimen, who would only have to take one tablet a day with Biktarvy as opposed to four or five

tablets on their current multiple-tablet regimen. The Subcommittee noted that single tablet regimens have rapidly taken over the market share in Australia.

8.15. The Subcommittee noted that most HIV patients are on a once daily dosing and considered that the number of tablets does not have an effect on compliance. The Subcommittee considered that the option of a single-tablet regimen would not have a noticeable impact on treatment adherence, as most HIV patients already have well controlled viral suppression.

8.16. The Subcommittee noted that most other antiretroviral HIV treatments may be significantly cheaper than bictegravir/emtricitabine/tenofovir alafenamide, and that it is highly likely that many patients currently taking these treatments would switch to bictegravir/emtricitabine/tenofovir alafenamide should it become available, on the basis of patient preference for a single-tablet regimen, and the perceived benefit of taking the most recently available treatment. The Subcommittee considered that as this would incur a significant cost to the health system, it would be feasible to fund bictegravir/emtricitabine/tenofovir alafenamide only if it was cost-neutral to the weighted cost of all other antiretroviral HIV treatments. The Subcommittee also considered that future price reductions of comparator drugs as they come off patent should be taken into account when considering health system costs and savings.

8.17. The Committee noted that in the supplier's cost minimisation model, they had reduced monitoring costs for bictegravir/emtricitabine/tenofovir alafenamide compared to other drugs. The Committee considered it unlikely that monitoring costs would be reduced as patients would have to undergo all the same tests with bictegravir/emtricitabine/tenofovir alafenamide as with other antiretrovirals.