Record of the Anti-infective Advisory Committee Meeting held on 13 June 2024

*This meeting was held as **hybrid** – members attended in person and virtually.*

Anti-infective Advisory Committee records are published in accordance with the Terms of Reference for the Specialist Advisory Committees 2021.

Note that this document is not necessarily a complete record of the Anti-infective **Advisory Committee meeting**; only the relevant portions of the meeting record relating to Anti-infective Advisory Committee discussions about an application or Pharmac staff proposal that contain a recommendation are generally published.

The Anti-infective Advisory Committee 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.

Pharmac Advisory Committees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Advisory Committee meeting will be reviewed by PTAC at an upcoming meeting.

Specialist Advisory Committees 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 Specialist Advisory Committees, 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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1. Attendance

Present
Rhiannon Braund (Chair)
Eamon Duffy
Elizabeth Dennett
Emma Best
James Chisnall
Nigel Raymond
Sarah McLean-Orsborn
Simon Briggs
Simon Dalton
Susan Morpeth

Apologies
Ed Gane (attended for the Therapeutic Group Review)
Jane Morgan
Sean Hanna

2. Summary of recommendations

Pharmaceutical and Indication	Recommendation
• Bictegravir 50 mg/Emtricitabine 200 mg/Tenofovir alafenamide 25 mg (Biktarvy) within the context of treatments for infections subject to Special Authority criteria.	Cost Neutral
• Pretomanid within the context of treatments for infection subject to Special Authority criteria.	High Priority

3. The role of Specialist Advisory Committees and records of meetings

3.1. This meeting record of the Anti-infective Advisory Committee is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) 2021 and Specialist Advisory Committees 2021.Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of Specialist Advisory Committees and PTAC.

3.2. Conflicts of Interest are described and managed in accordance with section 6.4 of the SAC Terms of Reference.

3.3. The Anti-infective Advisory Committee is a Specialist Advisory Committee of Pharmac. The Anti-infective Advisory Committee and PTAC and other Specialist Advisory Committees have complementary roles, expertise, experience, and perspectives. The Anti-infective Advisory Committee and other Specialist Advisory Committees may therefore, at times, make recommendations for treatments for anti-microbials 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-microbials that differ from the Anti-infective Advisory Committee's, or Specialist Advisory Committees may make recommendations that differ from other Specialist Advisory Committees'.

Pharmac considers the recommendations provided by both the Anti-infective Advisory Committee and PTAC and any other relevant Specialist Advisory Committees when assessing applications for treatments for anti-microbials.

4. Welcome and introduction

4.1. The chair welcomed the committee with a karakia, followed by whakawhanaungatanga.

5. Record of Anti-Infective meeting held Thursday, September 22, 2022

5.1. The Advisory Committee reviewed the minutes of the Anti-Infective Advisory Committee meeting held on Thursday, 22 September 2022 and agreed that the minutes be accepted.

6. Previous action points/recommendations made

6.1. The Committee considered ongoing work by Pharmac staff to remove prescriber restrictions from the schedule, noting that the intent of the work was to remove

restrictions from the Pharmaceutical Schedule that constituted clinical advice, as the schedule is intended as a funding tool rather than to support clinical practice.

6.2. Members noted that removal of restrictions around medicines access was generally equity positive but that in the Anti-infectives space specifically there were substantial antimicrobial resistance (AMR) concerns, as funding restrictions were one of the primary 'hard' ways to drive the appropriate use of medicines.

6.3. The Committee noted that since the previous meeting of the Anti-infective Advisory Committee Pharmac had implemented a parallel assessment process for medicines that were not yet Medsafe registered.

6.4. The Committee noted the record of the previous Anti-infective Advisory Committee held in September 2022.

6.5. The Committee considered action points from previous meetings. The Committee noted the previous recommendation to amend restrictions for azithromycin by replacing the current restrictions with indication specific Special Authority criteria. The Committee reiterated its continued support for further restrictions on azithromycin use and noted that typhoid disease should be included in the proposed list of restrictions, noting that treatment of *Salmonella typhi* was cost-saving to the health sector as it prevented hospitalisations.

6.6. The Committee noted previous considerations of antibiotics for non-cystic fibrosis bronchiectasis. The Committee noted the considerations of the Respiratory Advisory Committee in 2022 (item 4.33) and that Pharmac staff had proposed a joint meeting of the Respiratory and Anti-infectives advisory committees to discuss the recommendations for treatment.

6.7. The Committee noted previous considerations for vancomycin capsules. The Committee reiterated its support for Pharmac continuing to seek a supplier, noting the suitability advantages and pharmacy time savings for a funded capsule/tablet over the current usage of oral liquid compounded from the funded injectable presentation.

6.8. The Committee considered the possibility of listing a Section 29 vancomycin product, but noted there were significant practical issues with Section 29 products. Members also noted that Section 29 products were often confusing for patients and could cause distress to people who felt that they may be receiving a lower quality or unsafe product. This was compounded in some high need populations such as refugees, where language barriers could be a significant issue in making the required disclosures for use of a Section 29 product.

6.9. The Committee noted that oral vancomycin for treatment of *Clostridium difficile* was the current standard of care, and considered that New Zealand was lagging behind international comparators in the lack of a funded oral capsule or tablet. Members noted that this was one of a significant number of medicines in where the lack of a Medsafe-approved product was a barrier to good clinical practice, and considered that Pharmac should continue to engage with both Medsafe and suppliers to progress a listing of vancomycin oral tablets or capsules.

6.10. The Committee considered its previous recommendation for widened access to antifungals for invasive fungal infections and noted the recommendation by the Cancer Treatments Advisory Committee in April 2023 (item 6) for a simplified Special Authority. The Committee noted its continued support for funding of this proposal.

6.11. The Committee noted its previous recommendation that ceftazidime with avibactam be funded for the treatment of carbapenem-resistant *Enterobacteriaceae*. The Committee noted its ongoing support for the funding of this item, and that in many hospitals it was already effectively in use via Pharmac exceptional circumstances pathways.

6.12. The Committee noted its previous considerations around obtaining dispensing data for pharmacist-only medicines (trimethoprim, nitrofurantoin) for urinary tract infections (UTIs). Members noted that the data may be recorded under the MDR and could be available as part of this data collection.

6.13. The Committee considered that non-funding of pharmacist prescribed empiric antibiotics for UTIs was inequitable and contributed to increases in Emergency Department presentations, due to difficulty in accessing primary care treatment. Members supported widening funding to include pharmacist-dispensed medicines for UTIs, but noted that the largest cost involved in Pharmacist lead treatment was usually the consultation fee, and recommended that Pharmac consult with Health New Zealand on potential options to fund pharmacist-lead empiric antibiotics for UTIs.

6.14. The Committee noted the funding of cefazolin 2 gram vials in October 2023.

6.15. The Committee noted Special Authority changes to widen access to ivermectin tablets were implemented in 2023 and 2024.

6.16. The Committee noted its ongoing support for the need to fund and equitably supply an oral liquid valganciclovir product across New Zealand.

7. Therapeutic Group and NPPA Review

7.1. The Committee reviewed the overall expenditure of the Infections – agents for systemic use Therapeutic Group and the high cost medicines within the group.

7.2. The Committee reviewed the individual subgroups of the Infections – agents for systemic use Therapeutic Group.

Anthelminthics

7.3. Members noted that the supplier of praziquantel had notified Pharmac of their intent to discontinue the product.

Systemic Antifungals

7.4. The Committee noted a reduction in overall expenditure for this group, largely due to the reduction in price of posaconazole.

7.5. Members noted that isavuconazole was not currently funded but that availability would be useful for the management of patients with resistant invasive fungal infections and renal failure. Members noted that posaconazole was usually initiated as IV treatment but was less suitable for these people as its formulations take several days to achieve a steady state, which could have significant negative outcomes. Members also noted that the intravenous formulation of isavuconazole is cyclodextrin-free which gives isavuconazole an advantage over other azole antifungals that require cyclodextrin because of the potential for nephrotoxicity from cyclodextrin.

7.6. The Committee noted that itraconazole oral liquid is expected to be discontinued in November 2024. Members noted feedback from the compounding working group (CWG) that itraconazole oral liquid compounded from tablets had low bioavailability and was appreciably less suitable than the proprietary oral liquid. The proprietary product contains cyclodextrin, which could not be easily introduced as part of the compounding process.

7.7. The Committee noted the feedback on itraconazole oral liquid from the Dermatology Advisory Committee in 2023. The Committee considered that dermatophytes would be sensitive to most alternatives but that many prescribers were more familiar and comfortable with itraconazole's use and that availability of supply would be beneficial, but it was not unmanageable if supply ceased. Voriconazole oral liquid was noted as an alternative for many uses but that the majority of prescribers would not be familiar

with its use in paediatrics. Members did not have any objections to future supply of itraconazole oral liquid as a section 29 product.

7.8. The Committee considered that any changes to the voriconazole oral liquid Special Authority criteria should include access for people with congenital immune deficiencies.

7.9. Members considered potential impacts from the widened access to antifungals for prophylaxis in severely immunocompromised people at high risk of fungal infection. Members noted that the majority of use would be azole antifungals for adults, with the exception being people with liver impairment that precluded azole antifungals, who would receive caspofungin or amphotericin B liposomal. Members noted that for paediatrics that the majority of children would preferably be on oral liquid voriconazole, but that children (or adults following paediatric protocols) with leukaemia were unable to receive azole antifungals due to commonly used drug interactions, primarily with vincristine. Most of these patients would be on caspofungin with a minority on amphotericin B liposomal.

Antimalarials / Antiparasitics

7.10. The Committee noted that ivermectin tablet usage had increased substantially since 2022. The increase was considered to be primarily driven by supply issues with topical scabies treatments and the simplified access to ivermectin as a second line treatment in response to these issues. Members considered that the current ivermectin Special Authority was appropriate and did not require amendment.

7.11. Members noted anecdotal reports from primary care that lack of response to permethrin in scabies was becoming more common and that a lack of an alternative topical treatment may be driving people to use ivermectin.

7.12. The Committee noted that moxidectin topical agent was an emerging treatment for scabies.

7.13. The Committee noted that artesunate was funded as ‘any brand’ on the HML and it was the ‘go-to’ agent for the intermittent severe malaria cases that present in New Zealand (primarily in people recently arrived or returned travellers). Members considered that continuity of supply was important for this agent and that when required it was needed urgently, and that there was a requirement for supply to be held in-country.

Antibacterials

7.14. Members noted an increase in overall usage of cephalosporins when compared to the other classes of antibiotics.

Antituberculotics and Antileprotics

7.15. Members noted that there was a small number of community approvals for linezolid since the widening of access for multi-drug resistant tuberculosis (MDR-TB) in June 2023 that exceeded the number of MDR-TB patients.

7.16. The Committee considered that there were appropriate non-tuberculosis uses for linezolid in the community and that the Special Authority should be extended to include specific indications. The Committee recommended the exact list of indications be addressed outside the current meeting in the interests of time.

7.17. The Committee reviewed correspondence from the Tuberculosis Clinical Network (TBCN) regarding new medicines and fixed dose combinations of interest in the New Zealand context. Members noted that due to the low number of cases and limited uses, Medsafe registration for these products would be difficult to achieve.

7.18. The Committee were advised that previously the Pharmacology and Therapeutics Advisory Committee (PTAC) and other Specialist Advisory Committees had reviewed

evidence for adherence benefits for fixed dose combinations in general and had concluded that such benefits were minimal. The Committee considered that while strong evidence of substantial benefit was lacking for fixed dose tuberculosis regimens this was generally true for adults, but that for children and adolescents, especially in the context of tuberculosis treatment there were significant advantages with reducing the number and frequency of doses. Members considered that, because tuberculosis treatment often involves a large number of tablets taken every day, the burden on children's caregivers was substantial as young children with TB can take a substantial amount of time (30 minutes to two hours) each morning for syrups / crushed tablets to be consumed. Incomplete treatment due to administration difficulties could drive the emergence of resistant tuberculosis infections.

7.19. The Committee noted that clinical experience with antiretroviral therapy with adults indicated that once daily better tolerated regimens have led to greatly improved adherence and disease control and that combination tablets were an important part of delivering this. Members considered this was also pertinent for children and adolescents. Lesser numbers of tablets are preferred by patients, but improvement of outcomes when the medicines and frequency of dosing were identical (i.e. one tablet once daily vs two to three tablets once daily) was difficult to evidence.

7.20. The Committee recommended that Pharmac should pursue options for funding of the medicines requested by the TBCN and that Section 29 listings were acceptable if required.

Cephalosporins and Cephamycins

7.21. The Committee noted a significant uplift in the volumes of cefalexin use over the 2023-24 period. Members noted that this may partially be due to capacity constraints in the healthcare system driving movement from IV antibiotics to oral options whenever possible, due to ease of administration and equivalent outcomes. Oral cefalexin has good bioavailability and tolerability and would be a medicine of choice for clinicians moving to high dose all-oral regimens. Members also noted a shift from flucloxacillin to cefalexin for skin infections and from trimethoprim for urinary tract infections in general practice. Members considered these changes may be due to an ongoing belief that flucloxacillin needed to be taken on an empty stomach, which complicated adherence, and to increasing resistance to trimethoprim.

7.22. Members noted that there was likely to be a gradual increase in cefalexin usage as more usage was shifted from wider spectrum antibiotics by updated prescribing guidelines.

Penicillins

7.23. Members noted that amoxicillin was widely used and that usage had increased approximately 20% since 2022, Members considered that this was likely due to movement from amoxicillin with clavulanic acid and from flucloxacillin.

Macrolides

7.24. The Committee noted that azithromycin 250 mg tablets had been unavailable since mid-2022. The Committee considered that there was an ongoing clinical need for a funded 250 mg azithromycin formulation due to limited alternatives for paediatrics, and noted that the currently funded 500 mg tablet was not scored or suitable for halving.

7.25. Members noted that new sore throat and rheumatic fever guidelines should be released shortly, which will include macrolide options for sore throat management in those with penicillin anaphylaxis.

Tetracyclines

7.26. The Committee reviewed the current Special Authority restrictions on tetracycline for the treatment of helicobacter pylori. The Committee recommended that the following renewal criteria be added to the tetracycline Special Authority (SA1332).

> **Renewal application** from any relevant practitioner
> Renewals valid for 3 months for applications meeting the following criteria:
>
> Both:
> 1. For the eradication of *Helicobacter pylori* following unsuccessful treatment with, or non-completion of second line therapy; and
> 2. For use only in combination with bismuth as part of a quadruple therapy regimen.

Other antibiotics

7.27. The Committee noted a request for funding of ciprofloxacin oral liquid in the community for cholangitis prophylaxis. Members noted this would be primarily for paediatrics and crushed tablets were not suitable for the requested group.

> **Special Authority for Subsidy**
> Initial application – (cholangitis prophylaxis) only from a Paediatrician or Gastroenterologist. Approvals valid for 6 months for applications meeting the following criterion:
> 1. The person is unable to use ciprofloxacin tablets or ciprofloxacin tablets are not suitable
>
> Renewal – (cholangitis prophylaxis) only from a Paediatrician or Gastroenterologist. Approvals valid for 6 months for applications meeting the following criterion:
> 1. Is unable to use ciprofloxacin tablets or ciprofloxacin tablets are not suitable

7.28. The Committee noted its support for the proposed Special Authority and that this would be a very small number of patients every year (<10) and thus while a Pharmaceutical Schedule listing would be preferred, managing via the NPPA process would be acceptable.

7.29. The Committee considered a proposal to amend the sulfadiazine sodium and pyrimethamine tablet restrictions for hospital and community to better reflect current best practice (additions in **bold**, deletions in ~~strikethrough~~):

> **Special Authority for Subsidy**
> Initial application from any relevant practitioner. Approvals valid without further renewal unless notified for applications meeting the following criteria:
> Any of the following:
> 1. For the treatment of toxoplasmosis in patients with HIV for a period of 3 months; or
> 2. For pregnant patients **with probable or confirmed toxoplasmosis** for the term of the pregnancy; or
> 3. For infants with congenital toxoplasmosis until 12 months of age~~.~~**; or**
> 4. **Both:**
>   - **4.1. For treatment or prophylaxis of toxoplasmosis in patients with a solid organ transplant or haematological malignancy; and**
>   - **4.2. Treatment or prophylaxis using trimethoprim with sulfamethoxazole is not appropriate**

7.30. The Committee recommended both the hospital indication restriction and Special Authority be amended to align with the proposed criteria.

Urinary tract infections

7.31. The Committee considered the continual increase in the usage of methenamine hippurate tablets for UTI prophylaxis, with approximately 500,000 tablets dispensed in the 2023/24 financial year (July-June). Members considered the usage was less concerning from an antimicrobial resistance perspective than other anti-infectives, as due to its mechanism of action, methenamine hippurate was unlikely to generate resistance.

7.32. Members considered that there was at present little evidence for long term safety signals for methenamine hippurate but that surveillance was warranted, as some

studies have explored the damage formaldehyde has on the urothelium of rat bladders with concern for the development of urothelial malignancy with long-term use.

7.33. The Committee noted Pharmac had recently received a notification from the supplier of nitrofurantoin 100 mg and 50 mg tablets that they will not be able to continue to supply the New Zealand Market. 100 mg tablets were in low supply but there was supply of the 50 mg tablets.

7.34. The Committee noted that at present there were three funded formulations of nitrofurantoin, 50 mg, 100 mg and 100 mg modified release (MR). Members noted that usage of the 100 mg had been decreasing since the funding of the 100 mg MR tablets.

7.35. Members noted that 100 mg MR tablets were not suitable for usage in children aged under 12 years. Members noted that restricting the 50 mg tablet usage to paediatrics until a long-term solution could be found was an option to preserve supply for this group.

7.36. The Committee recommended that Pharmac staff attempt to secure alternative supply of both 50 mg and 100 mg immediate release tablets. The Committee considered that continuity of supply of nitrofurantoin was a high priority, but that in practical terms the 100 mg tablets were not a necessity as they could be substituted by two 50 mg tablets.

HIV treatment and prophylaxis

7.37. The Committee reviewed correspondence from the Burnett Foundation on behalf of the National HIV and AIDS Forum.

7.38. The Committee considered the current Special Authority criteria for antiretrovirals for HIV. The Committee noted that the current structure of the Special Authority criteria for Post Exposure Prophylaxis (PEP) had the potential to cause confusion for pharmacists and prescribers. The Committee noted that technical schedule processing reasons prevented the placement of a medicine under multiple special authorities e.g. one for treatment and one for prophylaxis.

7.39. The Committee noted that the Ministry of Health | Manatū Hauora maintained a list of approved antiretroviral treatment prescribers and that this was an additional restriction on initiating treatment for HIV. The Committee noted correspondence received by Pharmac that the Ministry was considering the removal of this list.

7.40. The Committee recommended that Pharmac remove the Special Authority criteria from HIV medicines, noting that appropriate consultation would be required for the proposed change.

7.41. The Committee considered placing HIV medicines on stat (3 monthly) dispensing, which would allow three months to be dispensed to all patients at once. The Committee recommended that Pharmac place HIV medicines on stat dispensing, the Committee further noting that the arguments for access made in support of stat dispensing for antiretrovirals may apply to many other medicines, and recommended that Pharmac generally review its placement of medicines on monthly vs stat (3 monthly) dispensing.

7.42. The Committee noted that efavirenz (brand name Stocrin) 200 mg and 600 mg tablets were currently out of stock. The Committee noted that supply of an alternative to the 600 mg tablet had been procured by Pharmac and was currently supplied as a section 29 product.

7.43. The Committee considered that there were limited clinical reason for continuing to use efavirenz, noting the presence of alternative antiretrovirals. However, the Committee noted that there were likely a small number of treatment experienced

patients who would have very limited or no funded alternatives. The Committee recommended that Pharmac consult on the requirement for continued supply.

Herpesvirus and Hepatitis B treatments

7.44. The Committee had no comment on these subgroups.

Hepatitis C treatments

7.45. The Committee noted that glecaprevir with pibrentasvir (Maviret) had undergone a change of prescription restrictions by the Medicines Classification Committee (MCC). The intent of the change was to allow nurse prescribers and pharmacists to prescribe glecaprevir with pibrentasvir for the treatment of Hepatitis C. The Committee considered that Pharmac should continue to support the work by the Ministry of Health | Manatū Hauora and Health New Zealand | Te Whatu Ora to enable nurse and pharmacist led prescription and dispensing of this medicine.

7.46. Members noted that glecaprevir with pibrentasvir usage had plateaued since 2022, but that that there was likely still a large pool of people, estimated to be 20,000 to 25,000, in New Zealand with undiagnosed Hepatitis C infection.

7.47. Members noted that all people who had experienced Maviret treatment failure were treated via the ongoing open-label trial for Hepatitis C retreatment using Maviret plus sofosbuvir Funding for this trial was concluding and future patients would need access to a funded medicine for retreatment, as per the previous discussions of the Committee in 2022. Members noted that the majority of Maviret treatment failures were caused by NS5A resistance, and that 90 people had been treated to date. Members also noted that the sofosbuvir used in the trial was to expire at the end of 2024, so an alternative funded medicine was required soon.

Other antiviral treatments

7.48. The Committee noted its continued support for regularisation of the ribavirin supply via a pharmaceutical schedule listing, noting that the current arrangements complicated access to the medicine when it was needed.

8. NPPA Applications

8.1. The Committee noted the previous consideration of pristinamycin at the 2022 meeting and detailed usage data provided by Pharmac. Members considered NPPA usage was driven by the lack of a Medsafe registered product.

8.2. The Committee noted a number of letermovir applications, and that they were for a specific subgroup of patients not specifically under consideration for listing on the wider pharmaceutical schedule.

9. Bictegravir, emtricitabine and tenofovir alafenamide for the treatment of HIV-1 infection in adults

Application

9.1. The Advisory Committee reviewed the application for, and correspondence from the Supplier of bictegravir with emtricitabine and tenofovir alafenamide for the treatment of HIV-1 infection in adults.

9.2. The Advisory Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

9.3. The Advisory Committee affirmed its previous recommendation **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.

9.3.1. In affirming this recommendation, the Committee considered there to be an unmet health need for people living with both HIV and chronic hepatitis B who are unable to tolerate tenofovir disoproxil dimethyl fumarate (TDF) which would be addressed if tenofovir alafenamide (TAF) was available and that it did not necessarily need to be in the bictegravir, emtricitabine and tenofovir alafenamide (BIC/FTC/TAF) combination pill.

Discussion

Background

9.4. The Committee noted that at its September 2020 meeting, it assessed bictegravir, emtricitabine and tenofovir alafenamide (BIC/FTC/TAF) and recommended that BIC/FTC/TAF be listed as cost neutral to the weighted price of all currently funded HIV treatments. At the time, the Committee considered:

9.4.1. there was no unmet health need for HIV patients in New Zealand as currently funded HIV medications are effective, readily available and suitable.

9.4.2. bictegravir/emtricitabine/tenofovir alafenamide has not demonstrated any superior efficacy compared to other currently funded HIV medications.

9.4.3. 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.

9.4.4. 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.

9.4.5. funding of bictegravir/emtricitabine/tenofovir alafenamide may have a large cost implication to the health system.

9.5. The Committee noted that a single tablet regimen, dolutegravir with lamivudine was listed from 1 May 2024 on the Pharmaceutical Schedule for the treatment of HIV. The application was assessed by the Committee in September 2022, when it recommended that dolutegravir with lamivudine single tablet regimen be listed as cost-neutral to the expected expenditure on HIV treatment regimens that dolutegravir with lamivudine would replace.

Health need

9.6. The Committee noted their previous discussions of the health need of people living with HIV when assessing BIC/FTC/TAF and dolutegravir with lamivudine (DTG/3TC).

9.7. The Committee considered that people living with HIV with renal impairment, at risk of renal impairment, low bone mineral density or cardiovascular disease resulting from TDF treatment are more likely to receive dolutegravir with lamivudine, others will be using multi-tablet regimens.

9.8. The Committee considered that for people living with both HIV and chronic hepatitis B who cannot tolerate TDF there is an unmet health need. The Committee considered there to be less than five people in the country who had this particular unmet health need that would be met by TAF, and that it was reasonable that this group could be treated via the Pharmac exceptional circumstances (NPPA) pathway.

Health benefit

9.9. The Committee noted their previous discussion of the health benefit of people living with HIV, in which they considered the following studies:

9.9.1. Sax et al. Lancet. 2017;390:2073-2082

9.9.2. Stellbrink et al. Lancet HIV. 2019; 6:e364-e372

9.9.3. Gallant et al. Lancet. 2017;390(10107):2063-2072

9.9.4. Wohl et al. Lancet HIV. 2019; 6(6):e355-e363

9.9.5. Molina et al. Lancet HIV. 2018;5:e357-e365

9.9.6. Daar et al. Lancet HIV. 2018;5:e347-e356:

9.9.7. Wohl et al. Patient. 2018;11:561-573

9.10. The Committee noted the further following studies:

9.10.1. Orkin et al. Lancet HIV. 2020;7:e389-e400

9.10.2. Orkin et al. AIDS. 2024;38:983-991

9.10.3. Sax et al. Clin Infect Dis. 2021;7:e485-e493.

9.10.4. Acosta et al. J Acquir Immune Defic Syndr. 2020;8:363-371.

9.10.5. Hagins et al. J Acquir Immune Defic Syndr. 2021;88:86-95.

9.10.6. Cossarizza et al. Front Immunol.2023:14:1279390.

9.10.7. Scevola et al. J Infect Dis. 2023;228:919-925.

9.10.8. Rodriguez et al. Lancet HIV. 2024;11:e300-e308

9.10.9. Cahn et al. J Aquir Immune Defic Syndr 2020; 83:310-3182020

9.10.10. Venter & Hill. Lancet. 2020;7:e374-5

9.10.11. Venter et al. N E Med J. 2019; 381: 803-15

9.10.12. Venter et al. Lancet HIV. 2020;7:e666–76

9.11. The Committee reiterated their consideration that the clinical evidence showed BIC/FTC/TAF has potent antiviral activity and that it is non-inferior to currently available HIV antiretroviral treatments.

9.12. The Committee noted the Sax et al. Clin Infect Dis. 2020;71:1380-9 pooled analysis, which included 5680 people living with HIV who had not previously received treatment. The study reported:

9.12.1. Integrase strand transfer inhibitors and TAF were found to be independent risk factors for weight gain.

9.12.2. Changing away from a TDF or efavirenz containing combination were also found to be risk factors.

9.13. The Committee considered that TAF is associated with a lower risk of renal impairment and smaller decreases in bone mineral density compared to TDF.

9.14. The Committee considered that people receiving TAF have been found to have higher levels of low-density lipoproteins (LDL) and high-density lipoproteins (HDL) cholesterol and triglycerides, however their total cholesterol-to-HDL ratio did not differ. The Committee considered that it was unknown if these metabolite changes are clinically significant.

9.15. The Committee considered that TAF may offer a health benefit for people with renal impairment, at risk of risk impairment, or with low bone mineral density. The

Committee considered the health benefit from for people with cardiovascular disease to be uncertain. The Committee considered there was a potential risk of weight gain for all people who receive TAF.

9.16. The Committee considered that TAF would provide the most health benefit for people living with both HIV and chronic hepatitis B who cannot tolerate TDF. The Committee considered the health benefit was provided by TAF and this does not necessarily need to be the BIC/FTC/TAF combination tablet.

Suitability

9.17. The Committee noted the Chastek et al. 2022. Conference Poster P103, HIV Glasgow presentation which reported the regimen persistence (treatment not being discontinued or switched) for 4,251 people living with HIV from the Optum Research Database. The presentation noted that:

9.17.1. Discontinuation of medicine (gap in treatment for ≥ 60 days) was 15% for multi-tablet regimes and 11% for single tablet regimes (p= 0.003).

9.17.2. The switching of medicines was 25% for multi-tablet regimens and 7% for single-tablet regimes (p< 0.001).

9.18. The Committee considered that switching regimens was not an important outcome as this did not affect the person's continuation of treatment.

9.19. The Committee considered that while discontinuation of medicine was an important outcome, that the evidence presented in this poster needed to be confirmed by other studies given that the data summarised in such conference poster presentations do not undergo peer-review.

Cost and savings

9.20. The Committee affirmed their previous statement that renal monitoring would remain much the same with TAF regimens as compared with TDF regimens. The Committee noted that patients normally had annual tests, and the frequency would not change if they were on a TAF regimen.

9.21. The Committee was informed that of the total patients receiving ART treatment at a single clinic in NZ (300+ patients, representing 10% of all people living with HIV in NZ), approximately 37% were receiving three drug regimens. The Committee considered approximately 72% of these patients (or 26% of the patients on any ART) would be interested in switching to BIC/FTC/TAF.

9.22. The Committee considered a potential market split if BIC/FTC/TAF were introduced to the market would be 60-70% DTG/3TC, 25-35% BIC/FTC/TAF, with 5-10% on other regimens.

Summary for assessment

9.23. The Advisory Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for BIC/FTC/TAF if it were to be funded in New Zealand for HIV. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Adults with HIV-1 infection.	Adults with HIV-1 infection and chronic hepatitis B who cannot tolerate TDF

Intervention	Bictegravir 50 mg with emtricitabine 200 mg and tenofovir alafenamide 25 mg. One tablet daily.	Bictegravir 50 mg with emtricitabine 200 mg and tenofovir alafenamide 25 mg. One tablet daily.
Comparator(s)* (NZ context)	• Emtricitabine 200 mg with tenofovir disoproxil 300 mg and dolutegravir 50 mg (FTC/TDF + DTG), two tablets daily; or • Abacavir sulphate 600 mg with lamivudine 300 mg and dolutegravir 50 mg (ABC/3TC + DTG), two tablets daily; or • Dolutegravir 50 mg with lamivudine 300 mg (DTG/3TC), one tablet daily.	• Dolutegravir 50 mg with lamivudine 300 mg (DTG/3TC), one tablet daily or a three-drug antiretroviral combination of the clinician's choosing PLUS entecavir
Outcome(s)	Non inferior efficacy.	Non inferior efficacy in the control of HIV virus Non inferior efficacy in the control of hepatitis B
Population: The target population for the pharmaceutical, including any population defining characteristics (eg. line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.		

10. Agents for multi-drug resistant organisms (MDROs)

Application

10.1. The Advisory Committee reviewed a request from the Ministry of Health | Manatū Hauora's National Reserve Supply Technical Advisory Group (MoH NRS TAG) for the funding of antimicrobials (ceftazidime-avibactam, ceftolozane-tazobactam, cefiderocol, aztreonam-avibactam, and intravenous minocycline) for multi-drug resistant organisms (MDROs).

10.2. The Advisory Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

10.3. The Advisory Committee **recommended** that the suggested antimicrobials (ceftazidime-avibactam, ceftolozane-tazobactam, cefiderocol, aztreonam-avibactam, and intravenous minocycline) be listed on Section H of the Pharmaceutical Schedule for MDRO infections, within the context of treatments for infections, subject to the following Hospital Restriction criteria:

> Restricted
> Clinical microbiologist or infectious disease specialist
> Either:
> 1. For treatment of proven resistant microorganism, based on microbiology reporting; or
> 2. Reasonably expected to be a resistant micro-organism considered to be susceptible to selected treatment.

10.4. In making this recommendation, the Advisory Committee considered the request for these medicines was based on expert opinion and experience in the New Zealand health system.

Discussion

Māori impact

10.5. The Committee discussed the impact of funding antimicrobials for the treatment of MDROs on Māori health areas of focus and Māori health outcomes. The Committee considered that given the small numbers of people expected to be treated by the suggested agents and the current lack of data, the impact on Māori is unclear but given inequity in high risk areas such as burns and use of ICU care, it is likely that inequities in the burden of disease exist.

Impact on Pacific peoples, disabled people, tāngata whaikaha Māori, and other people who have been underserved by the health system

10.6. The Committee discussed the impact of funding antimicrobials for MDRO infections on priority populations. The Committee considered that there was an inequitable burden on Pacific peoples when considering MDROs and members noted that Carbapenem-resistant *Acinetobacter* is a particular issue in some patients who arrive from Samoan or Fijian hospitals. The Committee considered that funding of these treatments would benefit Pacific peoples. The Committee considered that given the small numbers of people expected to be treated by the suggested agents the impact on other priority populations could not be determined.

Background

10.7. The Committee noted correspondence from the Ministry of Health National Reserve Supply Technical Advisory Group (MoH NRS TAG) requesting the following agents be listed for MDRO infections:

10.7.1. ceftazidime-avibactam

10.7.2. ceftolozane-tazobactam

10.7.3. cefiderocol

10.7.4. aztreonam-avibactam

10.7.5. intravenous minocycline

10.8. The Committee noted that ceftazidime with avibactam had already been assessed and ranked by Pharmac, based on the Committee's previous advice given at its May 2019 meeting. The Committee noted that Pharmac staff did not require any further advice on this application at this stage.

10.9. The Committee noted that the ceftolozane-tazobactam had been recommended for decline, based on the Committee's previous advice given at its May 2019 meeting. The Committee noted that this had received consultation feedback from two of its members concerning the need for this treatment for a small number of urgent multi-resistant infections under the supervision of an infectious disease specialist. That feedback included that there had been recent discussions with the Ministry of Health regarding an access pathway for the treatment of multi-drug resistant organisms; the possibility that the decline recommendation in 2019 may have been due to the limited published evidence for multi-drug resistant infections at that time; the use of this product is in hospitals in a small number of urgent multi-resistant infection cases mainly for microbiologically-confirmed MDRO infections on the advice of a clinical microbiologist or ID physician. The Committee noted that Pharmac staff are seeking further clinical advice on the progression of these applications to decline.

Health need

10.10. The Committee considered that people who have MDRO infections have a high health need and require access to appropriate treatments for these infections. The Committee considered that many of these infections currently occur in people who

have come to New Zealand from overseas where they have been colonised with a MDRO (eg Carbapenem-resistant *Acinetobacter* from Samoan or Fijian hospitals). The Committee considered that the exception to this would be multi-drug resistant *Pseudomonas aeruginosa* which is mostly generated by use of anti-microbials in people colonised with *Ps. aeruginosa*. The Committee considered that over the last three years these cases have increased with the lifting of COVID-19 border restrictions. The Committee considered that due to the nature of infection spread and development of resistance that this issue will persist and there is potential for these organisms to spread more widely in the New Zealand population.

10.11. The Committee considered that the proposed decline of funding of ceftolozane-tazobactam for treatment of MDROs was not appropriate and there is an unmet need for this treatment that would not be met by ceftazidime-avibactam and other funded antibiotics as previously advised. The Committee considered that the current application for ceftolozane-tazobactam for complicated intra-abdominal infections and complicated urinary tract infections in the close-out process could be progressed to declines. The Committee noted that the declining of applications did not limit new or future applications for the same medicines.

10.12. The Committee considered that people with MDRO infections require urgent care due to the nature of MDRO infections and that currently the identified antimicrobials are being used for MDRO infections in New Zealand hospitals under the rapid approval process for exceptional circumstances. The Committee considered that at the current time this responsibility falls to the individual prescriber or hospital, which had the potential to create inequities in care across New Zealand.

10.13. The Committee noted that the supply of these treatments varies as they are often sourced internationally. The Committee considered that this has significant impacts of the timely delivery of treatment, with some treatments having a lead time of up to four weeks. The Committee considered that contracting for these products would allow the timely supply and administration of treatment. The Committee considered that procuring treatments was challenging even for funded antimicrobials on Section H of the Pharmaceutical Schedule, where the hospital can source any brand. The Committee recommended that Pharmac engage with suppliers to ensure supply at a national level. The Committee noted that this is different to Pharmac's standard processes.

Health benefit

10.14. The Committee considered that ceftazidime-avibactam and aztreonam-avibactam would be appropriate to treat carbapenemase-producing *Enterobacterales* (CPE), and some susceptible *Pseudomonas aeruginosa*.

10.15. The Committee considered that ceftolozane-tazobactam would be appropriate to treat multi drug resistant *Pseudomonas aeruginosa*.

10.16. The Committee considered that cefiderocol would be appropriate to treat certain gram Gram-negative MDROs (CPE, carbapenem-resistant *Acinetobacter baumannii* (CRAB) and multi-drug resistant *Ps. aeruginosa*).

10.17. The Committee considered that intravenous minocycline would be appropriate to treat CRAB infections.

10.18. The Committee considered that while these considerations were relevant at the time of the meeting, they would likely change over time due to changes in antimicrobial resistance.

10.19. The Committee noted that there was a lack of data for the dosing and use of these agents in neonates and pregnant people.

10.20. Members considered that the following agents would also be useful to treat MDROs:

10.20.1. sulbactam-durlobactam

10.20.2. meropenem-vaborbactam

10.20.3. imipenem-relebactam

10.20.4. cefepime with zanibactam or taniborbactam

10.21. Members considered that in particular sulbactam-durlobactam should be sought by Pharmac for the treatment of MDROs, in particular carbapenem-resistant *Acinetobacter baumannii* (CRAB).

Funding criteria

10.22. The Committee noted that the treatment of people with MDROs was under supervision of an infectious disease physician or clinical microbiologist. The Committee considered that infectious disease specialists and clinical microbiologists were prudent in their use of antimicrobials, to reduce the risk of future resistance and development of MDROs. The Committee considered that it was appropriate to limit the funding of agents to these specialists on Section H.

10.23. The Committee considered that specifying "the treatment of suspected or proven multi-drug resistant organisms" would be sufficient to restrict use to the people who are most in need.

10.24. The Committee considered that these agents only need to be listed in Section H for use in hospital for MDROs.

Future consideration of MDRO treatments

10.25. The Committee noted that the antimicrobials considered for treatment of MDROs were proposed by the Ministry of Health | Manatū Hauora's NRS TAG. The Committee noted that the purpose of the NRS TAG is to ensure appropriate national reserves, including of anti-infective agents in case of an infectious disease outbreak. The Committee noted that this Group was time limited and would likely not continue to be supported. The Committee considered that if it (the Committee) was tasked to continue identifying treatments nationally for MDROs then annual review would be appropriate.

10.26. The Committee considered that it would be useful to assess utilisation patterns and wastage of these agents over the prior three years.

11. Matters arising: pretomanid for the treatment of multi-drug resistant tuberculosis and extensively drug-resistant tuberculosis

Application

11.1. The Advisory Committee reviewed the application for pretomanid for the treatment of multi-drug resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB).

11.2. The Advisory Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

11.3. The Advisory Committee recommended that **pretomanid** be listed with **high priority** within the context of treatments for infection subject to the following Special Authority criteria:

Proposed Special Authority Criteria
Initial application – multi-drug resistant tuberculosis
Application from any relevant practitioner. Approval valid for 6 months
Both:

1. The person has multi-drug resistant tuberculosis; and
2. A multidisciplinary network of relevant Specialists has reviewed the individual case and recommends pretomanid as part of the treatment regimen.

11.4. The Advisory Committee made this recommendation based on:

- The high health need of people with MDR-TB
- The good quality evidence demonstrating that pretomanid as part of the BPAL/M regime is effective, safe and requires a shorter duration of treatment, so the person and their whānau/family will be able to resume their normal daily activities sooner.
- Cost saving to the healthcare system.

11.5. The Advisory Committee recommended the length of approval for bedaquiline and linezolid (in the community) be aligned with that of pretomanid.

Discussion

Māori impact

11.6. The Committee discussed the impact of funding pretomanid for the treatment of TB on Pharmac's Hauora Arotahi: Māori health areas of focus and Māori health outcomes. The Committee noted Romaha Ora (respiratory health) is a Hauora Arotahi. The Committee noted Māori are disproportionately represented in new TB cases who were born in New Zealand, and there are Māori who have required treatment with MDR-TB agents.

Impact on Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been underserved by the health system

11.7. The Committee discussed the impact of funding pretomanid for the treatment of MDR-TB for Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been underserved by the health system.

- Pacific people are disproportionally represented in new TB cases who were born in New Zealand, and there are Pacific people who have required treatment with MDR-TB.
- People who live in the most socioeconomically deprived areas (NZDep2013 quintile 4 or 5) are disproportionally represented in new TB cases irrespective of birthplace.
- Refugees and people living in institutions, including immigration centres, prisons, rest homes and mental health facilities, are at high risk of being infected with TB.

Background

11.8. The Committee noted bedaquiline is listed on the Pharmaceutical Schedule for the management of multi-drug resistant tuberculosis (MDR-TB). The application was assessed by PTAC at its February 2020 meeting, where the Committee recommended that bedaquiline be funded with a high priority for the treatment of MDR-TB.

11.9. The Committee noted linezolid is listed on the Pharmaceutical Schedule for the management of MDR-TB. The application was assessed by the Anti-infectives Advisory Committee (previously Subcommittee) at its September 2020 meeting, where the Committee recommended that linezolid be funded with a high priority for the treatment of MDR-TB.

11.10. The Committee noted Pharmac has previously considered funding of pretomanid for treatment of MDR-TB through the Named Patient Pharmaceutical Assessment

(NPPA) pathway. To date there have been two applications for the treatment of MDR-TB for two individuals, both applications being approved.

Health need

11.11. The Committee noted the Cutfield et al. Intern Med J. 2022;52:1381-6 study reporting the annual rate of confirmed MDR-TB between 1989 and 2018 ranged from 1 to 7 cases. ESR reported that in 2020 there were four cases of MDR-TB (defined as resistance to at least isoniazid and rifampicin).

11.12. The Committee noted that the World Health Organization (WHO) recommends 3 regimes for the treatment of MDR-TB:

11.12.1. The BPAL/M regime compromising of bedaquiline, pretomanid, linezolid with moxifloxacin (BPaLM) for six months; if fluoroquinolone resistance is proven, the BPaL regime (without moxifloxacin) can be used for a total of 9 months.

11.12.2. The 9-month all-oral regimen comprised of bedaquiline (used for 6 months), in combination with a selection from levofloxacin/moxifloxacin, linezolid, ethambutol, isoniazid (high dose), pyrazinamide and clofazimine. The Committee considered this regime also may be used in New Zealand following the listing of bedaquiline and linezolid on the Pharmaceutical Schedule.

11.12.3. Longer drug regimens comprised of a selection of drugs from group A (levofloxacin/moxifloxacin, bedaquiline, linezolid), group B (clofazimine, cycloserine/terizidone), group C (ethambutol, delamanid, pyrazinamide, imipenem-cilastatin/meropenem, amikacin/streptomycin, ethionamide/prothionamide, *P*-aminosalicylic acid). The Committee noted the Guidelines for Tuberculosis Control in New Zealand, 2019 that reports treatment is usually continued for at least 18 months after culture conversion. The Committee considered these regimes to be associated with significant adverse effects, greater use of intravenous antibiotics and hospitalisation, and high cost. These regimens have needed to be used in New Zealand for the treatment of MDR-TB infections until availability of newer agents enabling use of the first two regimens.

11.13. The Committee noted that all people with MDR-TB commence treatment with daily observed therapy.

11.14. The Committee noted the Thomas et al. PLoS One. 2016;11:e0147397 systematic review which reported that MDR-TB has substantial impact on a person psychologically, socially and financially:

- The Committee noted that people with MDR-TB must isolate from others until it is confirmed by culture conversion that they are no longer infectious, and this often takes more than three months. The Committee considered that the person's whānau/family are at greatest risk of infection.
- The Committee considered that when receiving long term treatment people must change their lifestyle to accommodate the therapy, and in some cases the treatment side effects prevent a person from being able to work or reduces their income due to taking time off due to sickness.

11.15. The Committee noted Māori are disproportionately represented in new TB cases who were born in New Zealand. In 2020, 55.4% of TB cases among people born in NZ were Māori. The incidence of TB was 3.7 per 100,000 among Māori, 73.6% of Māori with TB were a part of a cluster. Similarly for 2016-2019 the incidence rate was 3.3 per 100,000 for Māori (ESR, 2020).Pharmac's dispensing data between July 2023-April 2024, reports that 3 people (23%) dispensed linezolid for the treatment of MDR-TB are Māori.

11.16. The Committee noted Pacific people are disproportionately represented in new TB cases, in 2020, the incidence rate of TB was 11.1 per 100,000 for Pacific people and 3.2 per 100,000 for Pacific people born in New Zealand and 75.3% of cases were a part of a cluster. Similarly, for 2016-2019, the incidence rate was 3.5 per 100,000 for Pacific people born in New Zealand (ESR, 2020).Pharmac's dispensing data between July 2023-April 2024, reports that 1 Pacific person (7%) was dispensed linezolid for the treatment of MDR-TB.

11.17. The Committee noted that 55% of new TB cases lived in the most socioeconomically deprived areas (NZDep2013 quintile 4 or 5) and the incidence of new TB cases in the most deprived quintiles was over twice the rate in the least deprived quintiles. Irrespective of birthplace (born in NZ/outside of NZ) a higher proportion of TB cases was reported from areas of greatest deprivation (ESR, 2020).

11.18. The Committee noted that people born outside of New Zealand accounted for 82% of new TB cases in 2020. 11.9% of new TB cases were diagnosed in the first year after arrival in New Zealand and 41.1% occurred withing five years (ESR, 2020).

11.19. The Committee noted that refugees and people living in institutions, including immigration centres, prisons, rest homes and mental health facilities, are at increased risk of being infected.

Health benefit

11.20. The Committee noted pretomanid is a nitroimidazooxazine that inhibits mycolic acid biosynthesis and thereby blocks mycobacterial cell-wall production, also acts as a respiratory poison against nonreplicating bacteria after nitric oxide release under anaerobic conditions.

11.21. The Committee noted a registration application for pretomanid has not been lodged with Medsafe.

11.22. The Committee noted pretomanid is a 200mg oral tablet that is taken once daily and is administered as part of BPAL/M regime.

11.23. The Committee noted the Conradie et al. N Engl J Med.2022;387:810-23 trial, which included 181 people with MDR-TB who were treated with the BPaL regime with varying dose and duration of linezolid (1200mg for 26 weeks, 1200 for 9 weeks, 600mg for 26 weeks or 600mg for 9 weeks).

- At the 72 week follow up unfavourable outcomes (treatment failure or disease relapse (clinical or bacteriologic)) occurred in 7% with 1200mg/26 weeks linezolid, 11% 1200mg/9 weeks, 9% 600mg/26 weeks and 16% 600mg/9 weeks.

11.24. The Committee noted the Nyang'wa et al. N Engl J Med. 2022;387:2331-43 trial, which included 301 people with MDR-TB who were treated with local standard of care, BPaL, BPaLM or BPaL with clofazimine.

- At the 8 week follow up, culture conversion (becoming non-infectious) had occurred in 77% with BPaLM, 67% BPaL+ clofazimine, 46% BPaL.
- At the72 week follow up unfavourable composite outcome (a composite of death, treatment failure, treatment discontinuation) occurred in 48% with local standard of care, 11% BPaLM, 19% BPaLC and 23% in BPaL.

11.25. The Committee noted the Conradie et al. N Engl J Med. 2020;382:893–902 trial, in which 109 people were treated with BPaL with the 1200mg linezolid dose administered once a day or 600mg twice per day.

- At the 6-month follow up after the completion of treatment unfavourable outcome (treatment failure (bacteriologic or clinical) or disease relapse) occurred in 10% of

the population (7 deaths, 1-consent withdrawal, 2 relapses during follow up, 1 loss to follow up).

- 89% (95% CI, 79 to 95) XDR had favourable outcome and 92% (95% CI, 79 to 98) MDR had favourable outcome.

11.26. The Committee noted the cohort comparison post-hoc study by Oelofse et al. Int J Tuberc Lung Dis. 2021;25:453-60 and the meta-analysis study by Hasan et al. Clin Infect Dis. 2024;78:730-74.

11.27. The Committee considered that when people with MDR-TB are treated with BPaL/M the time to culture conversion is shorter, there are greater proportions of people having successful treatment, lower rates of adverse events and less pill burden compared to the current standard of care.

11.28. The Committee considered that the faster time to culture conversion would mean people and their whānau/family can resume their normal daily living sooner.

11.29. The Committee considered that with the BPAL/M regime, health care resources (public health nurses, hospital clinical appointments, pharmacy for medication pick up, blood tests) will need to be used for shorter amounts of time and there may be less adverse drug reaction related hospital admissions.

Suitability

11.30. The Committee noted that BPaL/M regimes are not suitable for a person who could become, or is, pregnant. The Committee noted there is no data regarding the use of pretomanid in children (<14 years), or TB involving the central nervous system, osteoarticular TB and disseminated TB.

11.31. The Committee noted that pretomanid is an oral medication, however the tablets could be crushed for people who have difficulty swallowing tablets (Alffenaar et al. Int J Tuberc Lung Dis. 2022; 26: 1097–1100).

Cost and savings

11.32. The Committee consider that if pretomanid was listed on the Pharmaceutical Schedule the BPaL/M regime would become the first-line option for the treatment of MDR-TB and replace the individualised 18–20-month regimes and the 9-month all-oral regimen.

11.33. The Committee considered it was unclear whether the nine-month oral regimen had yet replaced the 18–24-month regimen in NZ.

11.34. The Committee considered the costs associated with direct observed therapy (DOT) to include the DOT observer, who are often nurses. The role of a DOT observer involves monitoring for side effects, overseeing lab tests, and providing support for people to attend clinic appointments, and often involves travel time to people's homes. The Committee noted not all DOT appointments were in person, with some taking place over video calls. The Committee considered that if the BPaL/M regime was used it would reduce the length of time these healthcare resources are needed.

11.35. The Committee considered that if the BPaL/M regime may reduce the need for inpatient hospital treatment, due to fewer adverse drug reactions when receiving treatment and shorter time to culture conversion (becoming non-infectious). The Committee considered there was no evidence from key trials to demonstrate this as treatment in those trials was outpatient based.

11.36. The Committee considered that currently there are likely 8 patients per year requiring treatment, however they expected this to gradually increase year-on-year.

Funding criteria

11.37. The Committee noted the Tuberculosis Clinical Network includes experts who provide advice to clinicians on how to appropriately treat a person.

Summary for assessment

11.38. The Advisory Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for pretomanid if it were to be funded in New Zealand for MDR and XDR-TB. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People with MDR-TB and XDR-TB
Intervention	Pretomanid 200 mg PO daily for 26 weeks, in conjunction with: • bedaquiline for 26 weeks (200 mg daily for 8 weeks, then 100 mg daily for 18 weeks • linezolid, 600mg once daily • moxifloxacin, 400mg once daily
Comparator(s)	9-month all-oral regimen comprises bedaquiline (used for 6 months), in combination with levofloxacin/moxifloxacin, linezolid, ethambutol, isoniazid (high dose), pyrazinamide and clofazimine OR 18–24-month regimen comprising of five antituberculotic medicines
Outcome(s)	• Faster resolution of TB infection. This may result in improved HRQoL. • Health system savings from reduction in DOT and possible shortened hospital stays in isolation necessary to ensure MDR-TB etc is no longer infectious before patient discharge back into the community. • Long-term health sector and public health effects of reducing the risk of untreatable XDR-TB antimicrobial resistance.
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

12. COVID-19 treatments

Content for review

12.1. The Advisory Committee was given information relating to funded COVID-19 treatments.

Discussion

12.2. The Committee noted that Pharmac is responsible for New Zealand's portfolio of COVID-19 treatments. The Committee noted that the portfolio has changed to focus on treatments that appear to have retained efficacy against extant COVID-19 variants. The Committee noted that previous clinical advice on the treatments has been received from Pharmac's COVID-19 Treatments Advisory Group. The Committee noted that budget for COVID-19 treatments is now included within the Combined Pharmaceuticals Budget.

12.3. The Committee noted that at the time of the meeting New Zealand's COVID-19 treatments portfolio included tocilizumab IV, remdesivir IV and oral nirmatrelvir with ritonavir. The Committee noted that molnupiravir was previously funded but was no

longer recommended or funded for use in New Zealand. The Committee noted that sotrovimab was previously recommended by the COVID-19 Treatments Advisory Group for funding but had not been available in New Zealand as Medsafe approval had not been completed. The Committee noted that tixagevimab with cilgavimab and casirivimab with imdevimab had been previously funded but experienced very limited use due to changes in efficacy against emerging SARS-CoV-2 variants and the expiry of stock before it could be used. Additional stock of these treatments have not been purchased by Pharmac.

12.4. The Committee noted that nirmatrelvir with ritonavir had been considered by the COVID-19 Treatments Advisory Group for Long COVID in May 2023 and December 2023. The Committee noted that the outcome of both reviews was to defer recommendation pending further information.

12.5. The Committee noted that dispensing counts for nirmatrelvir with ritonavir have varied over the last 6 months as the number and mix of cases has fluctuated. The Committee noted that there was also regional variability in dispensing reflective of the number of people in each region, their demographic characteristics affecting eligibility, and regional differences in COVID-19 attack rates. The Committee noted that numerically most of the dispensings were for people aged 65-84 years, reflecting oral nirmatrelvir with ritonavir being funded universally for any cases aged 65 years and over, in turn reflecting all older people with COVID-19 having a high risk of severe disease.

12.6. The Committee noted the community access criteria for COVID-19 treatments (nirmatrelvir with ritonavir) are extensive.

12.7. The Committee noted that currently Pharmac is working to align COVID-19 treatments' advice, assessment and funding processes with the standard processes for funding community pharmaceuticals. The Committee noted that any changes to the current funding of COVID-19 anti-viral treatments would be considered via Pharmac's normal processes, including public consultation and the consideration of feedback received. The Committee noted that this meant that future advice for COVID-19 treatments would be sought from the Anti-infectives Advisory Committee.
