Record of the Anti-infectives Advisory Committee Meeting held on 22 September 2022

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

Anti-infectives Advisory Committee records are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) Specialist Advisory Committees 2021.

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

The Anti-infectives 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.

Table of Contents

1. Attendance

Present
Rhiannon Braund (Chair)
Eamon Duffy
Ed Gane (parts of)
Elizabeth Dennett
Emma Best
Graham Mills
Howard Wilson
James Chisnall
Sean Hanna
Simon Briggs
Steve Chambers

Apologies
Anja Werno
Jane Morgan

2. Summary of recommendations

Pharmaceutical and Indication	Recommendation
• Antifungals for prophylaxis of invasive fungal infection (IFI) in patients with acute myeloblastic leukaemia (AML), acute lymphoblastic leukaemia (ALL), stem cell transplant (SCT) and graft vs host disease (GVHD)	Widening of Access
• Dolutegravir/lamivudine (DTG/3TC) for the treatment of Human Immunodeficiency Virus (HIV-1) infection in adults and adolescents (>12 years), who have no known or suspected resistance to either antiretroviral component Interests	Cost Neutral

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) and Specialist Advisory Committees 2021, available on the Pharmac website at https://pharmac.govt.nz/assets/2021-Specialist-Advisory-Committee-Terms-of-Reference.pdf. The 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 7.2 of the PTAC 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 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. Record of the Anti-infective Subcommittee meeting held September 22, 2020

4.1. The Committee noted several anti-infective funding proposals have been funded since the start of 2021, including the new listing of nitrofurantoin modified release tablets for urinary tract infections, palivizumab for RSV, widened access to antiretrovirals for pre-exposure prophylaxis of HIV (PrEP) and post-exposure prophylaxis of HIV (PEP), valganciclovir for cytomegalovirus prophylaxis and treatment in transplantation.

4.2. The Committee noted the following items recommended for funding at the previous Anti-infective Subcommittee meeting have been ranked on Pharmac's priority list for funding:

- Linezolid for multidrug-resistant tuberculosis (MDR-TB). The Committee noted that Pharmac was progressing this alongside listing bedaquiline for MDR-TB. Members also noted that the Schedule price for linezolid tablets was significantly higher than that paid by international authorities, specifically the UK.

- Rifampicin/isoniazid/pyrazinamide/ethambutol fixed-dose combination tablet.

- Letermovir for cytomegalovirus infection prophylaxis.

- Bictegravir/Emtricitabine/Tenofovir alafenamide fixed-dose combination for the treatment of HIV.

4.3. The Committee considered the following action points from previous meetings.

- Listing probenecid and cefazolin on PSO for cellulitis.
    - Members considered that the recommendation for inclusion of cefazolin on the PSO list did not need further action as new guidelines for cellulitis support the use of boosted oral therapy with oral antibiotics and probenecid instead.
    - Members considered that probenecid should be considered for inclusion on the PSO list.
    - Members noted that the funding model for cellulitis management needs to be changed to support the move to different (non-IV) therapies and noted that this could be considered by Te Whatu Ora.

- High expenditure on cephalosporins and lack of data on the indication cephalosporins are being used for.

- Members reiterated that such indication data would be of high value and that it could potentially be collected by practice management software.

- Pharmacist only usage of trimethoprim.

  - Members noted that lack of visibility of the usage levels from pharmacist only trimethoprim prescriptions made it difficult to accurately assess antibiotic usage for UTI's. While such data is not currently available, Members considered that funding pharmacist only dispensing of medicines should be investigated to allow collection of this data.

- Valganciclovir oral formulation.

  - Members noted that the unavailability of a commercial oral formulation was placing excess pressure on compounding pharmacies and that it was an issue with other oral liquids as well. Members noted that individuals with congenital CMV infection and those who are immunocompromised would require ongoing access and recommended that a commercial oral valganciclovir liquid be made available.

  - Members reiterated previous advice from 2019 that congenital CMV should be added to the Special Authority and hospital indication restrictions for valganciclovir after review of NPPA data.

4.4. The Committee reviewed the COVID-19 treatment related investments made by Pharmac as part of the response to the COVID-19 pandemic. The Committee noted that investments in this area were made from a separate budget allocated by the Government which means that COVID-19 treatment costs do not come from the combined pharmaceutical budget. Members noted that Pharmac has a separate COVID-19 Treatments Advisory Group and membership of this Group overlaps with that of this Committee.

4.5. The Committee noted that the clinical landscape for COVID-19 treatment has changed due to changing variants, vaccination, previous exposure and availability of treatments. The Committee considered that given the current state of the pandemic it would now be reasonable to reassess the previous assessment model for COVID-19 treatments which prioritised availability and provision of a separate portfolio of treatments.

5. Correspondence and Matters Arising

Correspondence: Ceftazidime with avibactam

5.1. The Advisory Committee noted the record of the previous meeting of the Anti-infective Advisory Committee in May 2019 which recommended that ceftazidime with avibactam (Zavicefta) be funded with a high priority subject to the following hospital indication restriction.

Restricted
Initiation
Clinical microbiologist or infectious disease specialist.
All of the following:
1. Proven resistant micro-organism, based on microbiology report; and
2. Proven infection with carbapenem-resistant Enterobacteriaceae (CRE); and
3. Ceftazidime with avibactam will not be used for prophylaxis; and
4. Treatment with colistin is clinically inappropriate.

Note: Where appropriate, treatment with ceftazidime with avibactam should be administered in combination with aztreonam, if available.

5.2. The Committee noted correspondence from the applicant (Pfizer New Zealand) which proposed changes to the hospital indication restriction based upon a number of international guidelines and scientific papers.

5.3. The Committee considered the proposed changes and noted that of the main point of difference proposed by the applicant was the inclusion of Pseudomonas aeruginosa with difficult-to-treat resistance (DTR-P. aeruginosa).

5.4. The Committee considered that items 3 and 4 of the proposed hospital indication restriction were not necessary to include in the restriction as in practice prophylactic use was unlikely and the potential for colistin use would be considered by the prescribing clinician.

5.5. The Committee noted that the number of people who would present with a susceptible DTR-P. aeruginosa infection for whom treatment with ceftazidime with avibactam would be appropriate would be very low due to differing mechanisms for resistance and the availability of funded alternatives for DTR-P. aeruginosa treatment. The Committee considered that it was unlikely that a pseudomonas infection would be susceptible.

5.6. The Committee considered that the Named Patient Pharmaceutical Application (NPPA) pathway would be the appropriate mechanism for provision of ceftazidime with avibactam to this patient group should no alternatives be available.

5.7. The Committee **recommended** that ceftazidime with avibactam be funded with a high priority subject to the following hospital indication restriction.

Restricted
Initiation
Clinical microbiologist or infectious disease specialist.
All of the following:
1. Proven resistant micro-organism, based on microbiology report; and
2. Proven infection with carbapenem-resistant Enterobacteriaceae (CRE)

Matters Arising: Cefazolin 2g vial – Surgical Antibacterial Prophylaxis

Discussion

5.8. The Committee noted that the cefazolin 2g vial for surgical antibacterial prophylaxis was considered by the Anti-Infective Subcommittee at its September 2020 meeting, in the context of:

5.9. 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.

5.10. A letter from the Health Quality and Safety Commission's Surgical Site Infection Improvement Programme which outlined that listing the 2 g vial would reduce the risk of contamination, time in dose preparation and waste in consumables and diluent used.

5.11. At that time, the Subcommittee had 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.

5.12. The Committee noted that cefazolin 500 mg vials and 1 g vials for injection are currently funded. The Subcommittee had 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 that 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.

5.13. The Committee noted that, while it is uncertain the exact proportion of 1g usage that would switch to 2g vials, estimates by Pharmac staff indicated the maximum incremental cost if all 1g usage was to be converted to 2g usage would be approximately $52,000 per year.

5.14. The Committee noted the following evidence:

- Morris et al. NZMJ. 2018;131:45-56
- Bratzler et al. Am J Health Syst Pharm. 2013;70:195-283
- Morris et al. Am J Health Syst Pharm. 2020;77:434-40
- Zimmerman and Shank. Am J Health Syst Pharm. 2020;77:408-9
- Morris et al. NZMJ. 2018;131:27-39
- Rondon et al. J Arthroplasty. 2018;33:3551-4
- Gow et al. NZMJ. 2016;129:51-8
- Morris et al. NZMJ. 2018;131:27-39
- Upton et al. NZMJ. 2005;118:U1316

5.15. The Committee noted the potential benefits that might be gained for the health system and patients from use of the 2g vial include: less syringe use, less preparation and administration time required in theatre, possible infection risk reduction plus potential reduction in post-operative infection risk (through supporting a national health quality initiative focusing on administering the right dose at the right time).

5.16. Given these potential benefits are likely to outweigh the cost of this presentation over that of the 1g vial, the Committee considered it would be reasonable for Pharmac to fund cefazolin 2g vial.

Matters Arising: Antifungals for prophylaxis of invasive fungal infection (IFI) in patients with acute myeloblastic leukaemia (AML), acute lymphoblastic leukaemia (ALL), stem cell transplant (SCT) and graft vs host disease (GVHD)

Application

5.17. The Advisory Committee reviewed the application for the prophylaxis of invasive fungal infections in those with AML and high risk or relapsed ALL and SCT until neutrophil recovery or resolution of GVHD for posaconazole and voriconazole.

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

Recommendation

5.19. The Advisory Committee recommended that access be widened to voriconazole and posaconazole for the prophylaxis of invasive fungal infections in those with high-risk

malignancies, lung and liver transplant recipients until neutrophil recovery or resolution of GVHD, with the changes to the Special Authority as follows:

Initial – (Invasive fungal infection prophylaxis) - Applications from any relevant practitioner.
Approvals valid for 3 months
Any of the following:

1. Prescribed by, or recommended by a haematologist, transplant physician or infectious disease specialist, or in accordance with a protocol or guideline that has been endorsed by the Te Whatu Ora Hospital in the specific settings where there is a greater than 10% risk of IFI; or
2. Both:
    2.1. Patient is to be treated with high dose (re)induction therapy or chemotherapy that is expected to result in prolonged neutropenia; and
    2.2. Any of the following:
        2.2.1. Patient has aplastic anaemia; or
        2.2.2. Patient is planned to receive a stem cell transplant; or
        2.2.3. Patient has a haematological malignancy eg ALL, AML, APML, HLH; or
3. Patient has received a lung or liver transplant and is at high risk of aspergillus infection

Renewal – **(Invasive fungal infection prophylaxis)** - Applications from any relevant practitioner.
Approvals valid for 3 months

Any of the following:

1. Prescribed by, or recommended by a haematologist, transplant physician or infectious disease specialist, or in accordance with a protocol or guideline that has been endorsed by the Te Whatu Ora Hospital in the specific settings where there is a greater than 10% risk of IFI; or
2. Patient is receiving a high-risk stem cell transplant; or
3. Patient has received a stem cell transplant and is receiving immunosuppression for GVHD*; or
4. Patient is still receiving therapy expected to result in prolonged neutropenia; or
5. Patient has received a lung or liver transplant and is still considered high risk for aspergillus infection; or
6. Both:
    6.1. Patient has previously received triazole prophylaxis during remission induction therapy; and
    6.2. Patient is to be treated with high dose re-induction therapy or consolidation therapy;

Note: * Graft versus host disease (GVHD) on significant immunosuppression is defined as acute GVHD, grade II to IV, or extensive chronic GVHD, or if they were being treated with intensive immunosuppressive therapy consisting of either high-dose corticosteroids (1 mg or greater per kilogram of body weight per day for patients with acute GVHD or 0.8 mg or greater per kilogram every other day for patients with chronic GVHD), antithymocyte globulin, or a combination of two or more immunosuppressive agents or types of treatment.

5.20. In making this recommendation, the Advisory Committee considered:

- These criteria are in line with current international guidelines and standards and current practice.
- Mould prophylaxis is only appropriate in those with a risk of >10% invasive fungal infection (IFI) and the conditions listed confer a >10% risk.
- Additional groups at high risk (>10% of IFI) include liver and lung transplant recipients at high risk of aspergillus

5.21. The Advisory Committee made additional **recommendations** that access be widened to amphotericin B liposomal injection and capsofungin for the prophylaxis of invasive fungal infections in those with high-risk haematological malignancies, lung and liver transplant until neutrophil recovery or resolution of GVHD and other complex surgeries, where triazole prophylaxis is not appropriate with the changes to the hospital restriction as follows:

Initial – (Invasive fungal infection prophylaxis) - Applications from any relevant practitioner.
Reassessment required after 6 weeks
Both:

1. Any of the following:
    1.1. Prescribed by, or recommended by a haematologist or infectious disease specialist, or in accordance with a protocol or guideline that has been endorsed by the Te Whatu Ora Hospital in the specific settings where there is a greater than 10% risk of IFI; or
    1.2. Both:
        1.2.1. Patient is to be treated with high dose induction therapy or re-induction therapy; and
        1.2.2. Any of the following:
            1.2.2.1. Patient has aplastic anaemia; or
            1.2.2.2. Patient is planned to receive a stem cell transplant and is at high risk for aspergillus infection; or
            1.2.2.3. Patient has a haematological malignancy eg ALL, AML, APML, HLH; or
    1.3. Patient has received a lung or liver transplant and is at high risk of aspergillus infection; or
    1.4. Patient is to have complex urological or thoracic procedures where fluconazole could not be used; and
2. Treatment with triazole antifungals is contraindicated or clinically inappropriate

Renewal – (Invasive fungal infection prophylaxis) - Applications from any relevant practitioner.
Reassessment required after 6 weeks
Both:

1. Any of the following:
    1.1. Prescribed by, or recommended by a haematologist, transplant physician or infectious disease specialist, or in accordance with a protocol or guideline that has been endorsed by the Te Whatu Ora Hospital in the specific settings where there is a greater than 10% risk of IFI; or
    1.2. Both:
        1.2.1. Patient has previously received posaconazole prophylaxis during remission induction therapy; and
        1.2.2. Patient is to be treated with high dose re-induction therapy or consolidation therapy; or
    1.3. Patient is receiving a high-risk stem cell transplant; or
    1.4. Patient has received a stem cell transplant and is receiving immunosuppression for GVHD*; or
    1.5. Patient has received a lung or liver transplant and is still considered high risk for aspergillus infection; and
2. Treatment with triazole antifungals remains clinically inappropriate.

Note: * Graft versus host disease (GVHD) on significant immunosuppression is defined as acute GVHD, grade II to IV, or extensive chronic GVHD, or if they were being treated with intensive immunosuppressive therapy consisting of either high-dose corticosteroids (1 mg or greater per kilogram of body weight per day for patients with acute GVHD or 0.8 mg or greater per kilogram every other day for patients with chronic GVHD), antithymocyte globulin, or a combination of two or more immunosuppressive agents or types of treatment.

5.22. In making this recommendation, the Advisory Committee considered:

- These criteria are in line with current international guidelines and standards and current practice.
- Mould prophylaxis is only appropriate in those with a >10% risk of invasive fungal infection (IFI) and the conditions listed confer a >10% risk.
- Additional groups at high risk (>10% of IFI) include liver and lung transplant recipients at high risk of aspergillus infection and those undergoing high risk urological or thoracic surgeries where fluconazole could not be used.
- That those that are unable to take azole antifungals due to contraindications had an unmet health need for prophylaxis for IFI.

Discussion

Māori Impact Statement

5.23. The Committee considered that the data on inequities associated with IFI in Māori was lacking. The Committee considered that Māori have higher rates of AML than non-Māori and treatment of AML is associated with risk of IFI.

Health Need

5.24. The Committee noted that voriconazole has been funded for treatment of IFI since 2012. It was also noted that posaconazole is currently funded for treatment of IFI and prophylaxis of IFI in people with AML and graft versus host disease (GVHD). The Committee noted that at the time of the meeting there was an exemption for the use of voriconazole and posaconazole in Auckland City Hospital and Starship Children's Hospital due to the increased risk of IFI associated with ongoing building works on the sites.

5.25. The Committee considered treatment for ALL has changed since prophylaxis of IFI was considered by the committee in 2012, such that the IFI risk during ALL treatment is now considered the same as that for AML. International guidelines (listed below) for prophylaxis of IFI in those with AML and ALL have also changed to reflect this.

- Teh BW, et al; Australasian Antifungal Guidelines Steering Committee. Consensus guidelines for antifungal prophylaxis in haematological malignancy and haemopoietic stem cell transplantation, 2021. Intern Med J. 2021 Nov;51 Suppl 7:67-88.
- Maertens JA, et al. European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European Conference on Infections in Leukaemia. J Antimicrob Chemother. 2018 Dec 1;73(12):3221-3230.
- Taplitz RA, et al. Antimicrobial Prophylaxis for Adult Patients With Cancer-Related Immunosuppression: ASCO and IDSA Clinical Practice Guideline Update. J Clin Oncol. 2018 Oct 20;36(30):3043-3054.
- Lehrnbecher T, et al. Clinical Practice Guideline for Systemic Antifungal Prophylaxis in Pediatric Patients With Cancer and Hematopoietic Stem-Cell Transplantation Recipients. J Clin Oncol. 2020 Sep 20;38(27):3205-3216.
- The Committee noted the following evidence for IFI prophylaxis in lung transplant recipients Pennington KM, et al. The Impact of Antifungal Prophylaxis in Lung Transplant Recipients. Ann Am Thorac Soc. 2021 Mar;18(3):468-476.

5.26. The Committee considered that the mortality and morbidity rates for IFI is high (mortality rate estimated at 20-35%) and there is also a significant burden on family/whānau. The Committee noted that comorbidities that pre-dispose people to IFI also could impact the estimated mortality rate.

5.27. The Committee noted that recommendations for prophylaxis are governed by risk of IFI. The Committee noted that this is stratified by risk of infection where low risk is considered <5% IFI risk and high risk is considered >10% IFI risk. The Committee noted that those with a risk of IFI>10% were recommended anti-mould prophylaxis.

5.28. The Committee considered that there are few funded agents for anti-mould prophylaxis for IFI. The Committee considered that this was a severe health condition (IFI) with significant unmet health need. The Committee also considered

that this was different to the prophylaxis for invasive candidiasis (yeast) for which fluconazole capsules were available without restriction. The Committee considered that there was value in having amphotericin B liposomal injection and caspofungin injection available under hospital restriction for prophylaxis of IFI where the use of azole antifungals is not appropriate. The Committee considered these groups to be those receiving vincristine in their treatment regimen, with significant mucositis, liver dysfunction, or post-surgery for liver or lung transplant as well as where cancer treatment protocols note drug interactions with azole antifungals.

5.29. The Committee considered that the proposed criteria for voriconazole and posaconazole were appropriate with an additional criterion restricting concurrent azole use. The Committee noted that amphotericin B liposomal and caspofungin injections were available for treatment of IFI, with minimal restriction, on the recommendation of an infectious disease specialist.

5.30. The Committee considered the significant health need of children with ALL at risk of IFI and noted there were no funded treatments for prophylaxis. The Committee considered this an unmet health need for children with ALL and those unable to swallow tablets due to the poor pharmacokinetic profile of the posaconazole liquid formulation, the need for it to be taken with a fatty meal to aid absorption and the difficulty reaching an adequate concentration before saturation of enteral absorption pathways.

5.31. The Committee considered that the following would be included in the group of conditions with a high risk (>10%) of IFI : allogeneic haemopoietic stem cell transplant (HSCT), AML or ALL induction, other haematologic malignancies with prolonged neutropenia (3-5 weeks) e.g. acute promyelocytic leukaemia (APML) or aplastic anaemia, GVHD on high dose corticosteroids (equivalent to 1 mg/kg prednisone) with neutropenia for over 1 week. The Committee considered these conditions to be high risk as per international guidelines (Australasian, US and European and Children's Oncology Group (COG) of which Starship Children's Hospital is a member). Other people identified with an unmet health need were those who had received lung and liver transplants. The Committee considered that, of the groups considered for funding, aspergillus infection in people with cystic fibrosis undergoing lung transplant and those undergoing high risk liver transplant or repeat transplant places them especially at risk of IFI.

Health Benefit

5.32. The Committee noted that the evidence for use of voriconazole and posaconazole in those who are immunocompromised is supported by international guidelines. The Committee considered that the body of evidence supporting these guidelines was significant and explicit. The Committee considered prophylaxis of IFI with voriconazole or posaconazole was the international standard. The Committee noted that three network meta-analyses found that there were no significant differences in efficacy of the oral forms of voriconazole and posaconazole (tablet only) but itraconazole was not considered equivalent due to its unreliable absorption.

- Lee CH, Lin C, Ho CL, Lin JC. Primary Fungal Prophylaxis in Hematological Malignancy: a Network Meta-Analysis of Randomized Controlled Trials. Antimicrob Agents Chemother. 2018 Jul 27;62(8):e00355-18

- Bow, E.J., Vanness, D.J., Slavin, M. et al. Systematic review and mixed treatment comparison meta-analysis of randomized clinical trials of primary oral

antifungal prophylaxis in allogeneic hematopoietic cell transplant recipients. BMC Infect Dis 15, 128 (2015)

- Zhao et al. Network Meta-analysis and Pharmacoeconomic Evaluation of Fluconazole, Itraconazole, Posaconazole, and Voriconazole in Invasive Fungal Infection Prophylaxis. Antimicrob Agents Chemother. 2015 Nov 2;60(1):376-86.

5.33. The Committee considered that the side effect profile of voriconazole was less desirable than posaconazole but both posaconazole and voriconazole were more acceptable than the currently funded liposomal amphotericin B.

5.34. The Committee considered that by reducing risk of IFI, especially in the treatment of children, there would be significantly less burden on their family/whānau resulting from less hospitalisations due to IFI.

5.35. The Committee considered that drug-drug interactions between triazoles and oncology agents, in particular vincristine, were a contraindication to use of triazoles for prophylaxis. The Committee considered evidence for alternative options was less robust however guidelines supported caspofungin and in some instances liposomal amphotericin B.

Suitability

5.36. The Group considered the impact of CYP2C19 on the metabolism of voriconazole and the need for therapeutic blood concentration monitoring in people taking voriconazole. The Committee noted that this was already in place for other indications. The Committee considered that variability of CYP2C19 phenotypes meant that there is up to 100-fold patient variability with voriconazole concentrations and clearance. The Committee considered the association of ethnicity and CYP2C19 phenotype and the potential for increased risk of toxicity in ethnicities who are more likely to be poor metaboliser phenotypes if not appropriately monitored. The Committee considered that although posaconazole has less interpatient variability therapeutic drug monitoring was still required.

5.37. The Committee noted that voriconazole is given twice daily in oral liquid, tablet and intravenous forms. The Committee considered the availability of these three formulations to be advantageous for community and hospital administration.

5.38. Posaconazole modified-release tablets are given once daily. The Group considered the oral posaconazole liquid to be unsuitable for use due to the requirement for high fat intake (15-50 g) with every dose. The Committee considered that this was not only unpalatable but particularly challenging in those with cancer where the majority of people have reduced appetite, mucositis or are on intravenous nutrition. The Committee considered that delisting the posaconazole oral liquid, after the listing of modified-release tablets, was appropriate due to the low use of the liquid, and concern with non-equivalent formulation selection error. The Committee noted that the intravenous formulation of posaconazole is not Medsafe registered in New Zealand and is not funded for use.

Cost and Savings

5.39. The Committee estimated that in people with ALL, three to four people a year would benefit from posaconazole for IFI and for those with aplastic anaemia, five to six people a year would benefit from posaconazole prophylaxis for IFI. The Committee considered that posaconazole would be used less in children. The Committee considered that it was suitable for use with other haematological malignancy

indications eg APML or HLH as they are also considered to be at high-risk of IFI. The Committee also considered that it was suitable to fund posaconazole for treatment of IFI for those that would be eligible for funded voriconazole treatment but where the fungal pathogen was resistant to voriconazole or where voriconazole is contraindicated. The Committee noted that currently there are only intravenous therapies (liposomal amphotericin B and caspofungin) funded in these instances. The Committee noted several approved NPPAs (Named Patient Pharmaceutical Application) for posaconazole use in these situations and considered that the restrictions could be extended to allow use of voriconazole and posaconazole for the rare circumstances where immunocompetent people have an invasive fungal infection.

5.40. The Committee considered that voriconazole use in the haematology setting for the prophylaxis of IFI would only occur in children. The Committee estimated the paediatric aplastic anaemia group to be five children per year and the high-risk ALL group to be 20 children per year within the Starship Children's Hospital service. The Committee considered that voriconazole would not be used in combination with other antifungals for the prophylaxis of IFI. The Committee considered that voriconazole would displace the majority of the use of amphotericin B in children as it is the preferred treatment except in children pre or post vincristine chemotherapy. The Committee considered that voriconazole prophylaxis for IFI would not be used in adult haematology patients unless they were unable to take posaconazole modified-release tablets.

5.41. The Committee considered the additional costs for the health sector to include cost for therapeutic blood monitoring whilst on treatment due to significant interpatient variability in metabolism by CYP2C19. The Committee also considered that pharmacogenomic testing could be used to assess CYP2C19 phenotype prior to prescription of voriconazole. The Committee noted that this is not used regularly within New Zealand and therapeutic blood monitoring is currently used to titrate the dose appropriately. The Committee considered neutrophil recovery following chemotherapy to take four weeks, however some indications would have a shorter period to neutrophil recovery.

Funding Criteria

5.42. The Committee considered the prescriber restriction within the criteria to be appropriate and considered that within a hospital setting that it was likely to be prescribed on the recommendation of a haematologist, transplant physician or infectious disease physician for those treated with high dose induction therapy or re-induction therapy for haematological malignancies, stem cell or solid organ transplant or aplastic anaemia.

5.43. The Committee considered that neutrophil recovery would take four weeks and that a 6-week reassessment would be appropriate after the initial application.

5.44. The Committee considered that the high-risk IFI group should be clearly identified in the funding criteria as those with a risk of >10% as described guidelines endorsed by Te Whatu Ora hospitals. The Committee considered that the specified conditions included in the criteria were all considered to have a risk >10% with the inclusion of those with ALL, aplastic anaemia and other haematological malignancy eg APML, HLH and lung or liver transplant at high risk for aspergillus infection.

5.45. The Group considered that those with ALL, AML, aplastic anaemia, and other haematological malignancies were considered at a risk of >10% of IFI if they were

being treated with high-dose remission induction therapy or re-introduction therapy or other chemotherapy expected to have a prolonged phase of neutropenia.

Summary of Assessment

5.46. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for voriconazole if it were to be funded in New Zealand for the prophylaxis of invasive fungal infections in those being treated for high-risk malignancies, lung or liver transplant recipients. 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 AML or ALL who are to be treated with high dose chemotherapy • People who have received a haemopoietic stem cell transplant, have graft versus host disease and are on immunosuppressive therapy. • People who have had a lung transplantation (and are colonised with aspergillus) • People who have had a liver transplant that is considered high-risk or is a re-operation
Intervention	*In adults*: Posaconazole modified-release tablet 300 mg daily or voriconazole 4-6mg/kg oral/IV twice daily until neutrophil recovery. *Most patients are likely to stay on Posaconazole.* *In children*: Voriconazole 9mg/kg oral/IV twice daily until neutrophil recovery. *Most patients are likely to switch to voriconazole*
Comparator(s) (NZ context)	*In adults*: Caspofungin 50-70mg IV daily until neutrophil recovery *In children*: Amphotericin B 1-5mg/kg daily to weekly OR caspofungin 25-50mg/m^2 IV daily
Outcome(s)	• No difference in fungal-free survival (FFS) compared to posaconazole or amphotericin B for patients who tolerate treatment • Reduced adverse events compared to amphotericin B • Potential suitability benefit compared to posaconazole in oncology patients who cannot swallow tablets and are unable to absorb the liquid formulation due to their limited appetite and low-fat intake

Table definitions:

Population: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup)

Intervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).

Comparator: 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).

Outcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.

6. Therapeutic Group Review

Discussion

6.1. The Committee reviewed the overall expenditure of the Anti-infectives Therapeutic Group and the highest expenditure pharmaceuticals.

6.2. The Committee noted that there had been a significant decline in usage of glecaprevir with pibrentasvir (Maviret) since its listing in 2019. Members noted that

this was primarily due to the reduction in known Hepatitis C cases due to treatment and limited diagnosis of new cases. Members noted that there remains a large undiagnosed population and if the ongoing “Stick it to HepC” testing programme in New Zealand is successful, this would likely significantly increase the usage of glecaprevir with pibrentasvir. This programme is part of the National Hepatitis C Action Plan for Aotearoa New Zealand, which has the goal of eliminating hepatitis C as a major health threat by 2030.

Subgroup Reviews

6.3. The Committee reviewed the usage in the subgroups of the Anti-infectives Therapeutic group.

Anthelmintics

6.4. The Committee noted a recent change in mebendazole brand to Vermox as the previous brand was discontinued by the supplier in March 2021. Vermox is under principal supply status until 30 June 2024.

Systemic Antifungals

6.5. The Committee noted that fluconazole and clindamycin usage had increased since the removal of restrictions in response to the COVID-19 pandemic and noted it would now be reasonable to review the removal of restrictions around systemic antifungals to ensure appropriate prescribing.

6.6. Members noted that itraconazole was primarily used for paediatric fungal head lesions and by immunologists as an alternative to voriconazole liquid but the oral liquid was restricted to congenital immune deficiency in the community. Members noted that fluconazole oral liquid or terbinafine oral solution would be another potential alternative to itraconazole, however fluconazole oral liquid currently has funding restrictions via Special Authority and would not be funded for community use for this purpose.

6.7. Members noted that itraconazole oral liquid may be used for treatment of fungal skin conditions and recommended that advice be sought from the Dermatology Advisory Committee on any discontinuation.

Antimalarials/Antiparasitics

6.8. The Committee noted feedback received by Pharmac that the ivermectin Special Authority criteria could be adjusted to remove the requirements to discuss the diagnosis of scabies with a dermatologist, infectious disease physician or clinical microbiologist to reduce the resource and time burden associated with the need to consult to fulfil the criteria.

6.9. The Committee noted that the diagnosis of scabies could be challenging. Members noted that ivermectin resistance amongst scabies was rare but that permethrin resistant scabies was relatively more common.

6.10. The Committee recommended that the specialist consultation requirement on ivermectin be removed and replaced with an indication-based restriction or endorsement. Members considered that this would improve access but not result in a change to the intended population and that any change should be linked with educational resources and sector communications to ensure the health sector was properly informed of the changes, including use in children.

6.11. The Committee noted the removal of quinine sulphate from the Schedule due to discontinuation by the supplier. The Committee had no concerns regarding the discontinuation and **recommended** that a replacement product not be sought, due to its side effect profile and limited uses.

Antituberculotics and Antileprotics

6.12. The Committee noted the previous recommendations for the listing of bedaquiline alongside linezolid for the treatment of multidrug-resistant tuberculosis (MDR-TB) and considered that the Special Authority recommended at the previous meeting remained appropriate.

Cephalosporins and Cephamycins

6.13. The Committee reviewed the usage of pharmaceuticals within the subgroup. The Committee noted cefaclor monohydrate usage in the community was unexpectedly high and that without indication data it was not possible to be certain of the reason. The Committee considered that cefalexin was more appropriate for most indications and noted that there was a trend of increasing cefalexin use while usage of cefaclor was gradually reducing.

6.14. The Committee considered that cefaclor was the most palatable of the second generation cephalosporins available as an oral liquid and that this could be driving usage especially amongst children.

6.15. The Committee reiterated its previous recommendation for oral probenecid to be made available on a practitioner supply order (PSO).

Penicillins

6.16. The Committee noted the discontinuation of procaine penicillin and had no further comments to make on the penicillins subgroup.

Macrolides

6.17. The Committee noted that roxithromycin dispersible 50mg tablets (Rulide-D) have been discontinued by the supplier and will be delisted from the Schedule in March 2023. The Committee noted that the national rheumatic fever and sore throat guidelines listed roxithromycin dispersible 50mg as a treatment, but that azithromycin was available as an alternative and 150mg and 300mg roxithromycin tablets remained available.

6.18. Members noted that in terms of its use in the community, older children might not require a dispersible tablet and the majority of its use would be for the treatment of community acquired pneumonia in children under 5 years of age who have a penicillin allergy. However, they noted that azithromycin liquid remained an alternative for these cases but that this resulted in an increased risk of anti-microbial resistance.

Tetracyclines

6.19. The Committee considered feedback from some clinicians regarding the need for renewal criteria for tetracycline for the treatment of H. Pylori, noting that a number of waiver applications for further courses of tetracycline had been received by Pharmac. Members requested further information be provided to members to inform an assessment of the need for repeat courses.

Other Antibiotics

6.20. Members noted the only available presentation of vancomycin is a 500mg vial for injection and that this presentation was also used for oral treatment of Clostridium difficile in the community. The current compounded formulation for community use is time consuming to prepare and has a relatively short shelf-life so imposes an additional demand on pharmacy resources. The Committee considered that Oral-sweet could be funded to facilitate the use of a compounded preparation with a longer shelf-life. The Committee noted that oral capsules of vancomycin would be appropriate for Clostridium difficile management in the vast majority of cases.

6.21. The Committee noted that vancomycin oral capsules were available internationally, which would address this issue, and that funding of this presentation should be considered by Pharmac.

6.22. The Committee also noted that increasing clindamycin use, since the removal of restrictions, may have resulted in increased community vancomycin use for Clostridium difficile management.

Urinary tract infections

6.23. The Committee noted an ongoing reduction in trimethoprim prescriptions for urinary tract infections (UTI) and a corresponding increase in nitrofurantoin modified release capsule prescriptions. Members expressed interest in seeing more complete data for UTI treatments from across the system, including those products that have been reclassified and provided direct to people as Pharmacist Only medicine.

6.24. The Committee noted that usage of methenamine hippurate for UTI prophylaxis was gradually increasing and that its usage may be bolstered by its availability for prophylaxis and a reluctance amongst physicians to prescribe antibiotics for long term use due to anti-microbial resistance (AMR).

6.25. The Committee noted that the evidence base for methenamine had been previously reviewed by PTAC and while the evidence for efficacy was limited, the AMR implications from increases in longer term antibiotic use were significant and that usage of methenamine was preferable in an AMR context.

6.26. The Committee considered potential uptake of fosfomycin for urinary tract infections (UTIs), noting the previous recommendation made at the prior meeting in September 2020 where it received a high priority recommendation.

6.27. The Committee noted that the estimate of 8200 people receiving Fosfomycin was likely an undercount and potentially did not include people who had experienced side effects to one or more other pharmaceuticals. Members considered this could be a significant group of people given the large number of people who experience UTIs.

6.28. Members noted that oral fosfomycin was already available in some locations via Primary Options for Acute Care (POAC) programmes and that estimates of numbers needing this could also be sourced from those programmes to inform Pharmac's assessment.

HIV Prophylaxis

6.29. The Committee considered a letter from the Burnett Foundation (previously the New Zealand AIDS Foundation) regarding the Special Authority criteria for Post Exposure

Prophylaxis (PEP) of HIV. Specifically, the request was to add vaginal intercourse to criterion 2.4 of the PEP criteria.

6.30. The Committee noted that the intent of the requested change was to be more inclusive of transgender men who have sex with men and non-binary people who have vaginal intercourse with Gay and Bisexual Men (GBM), and that currently there was a potential for these groups to be ineligible.

6.31. The Committee were supportive of the change in principle. Members noted that including all vaginal intercourse in the criteria would include heterosexual and cisgender women who were previously considered by the Committee to be in a low-risk group. The Committee also noted that Transgender women were considered a higher-risk group that may not be included under the current criteria.

6.32. The Committee **recommended** that the criteria be changed to include the groups requested by the Burnett Foundation and **recommended** that Pharmac consult with relevant stakeholders around changing the wording of the criteria to be inclusive of the identified groups and other potential high-risk groups without widening the criteria to include all vaginal intercourse.

HIV Antiretrovirals

6.33. The Committee noted that the supplier of efavirenz had notified Pharmac of its intent to discontinue supply of efavirenz 200mg and 600mg tablets. The Committee noted that total number of people on efavirenz was low and in decline, with less than 100 in the 2021/22 financial year. Members considered that need for continuity of supply for efavirenz was also low due to alternative, potentially more tolerable antiretrovirals being available and a low burden of resistance amongst the New Zealand HIV+ population. The Committee noted that there may be some hesitance amongst individuals who were stable on an antiretroviral regime involving efavirenz to change antiretroviral regimes, however in most cases regimes involving efavirenz were likely to be for older people who would eventually need to change due to the impacts of advancing age.

6.34. The Committee considered that Pharmac should investigate the patent expiry dates of tenofovir alafenamide (TAF) noting that it would be an appropriate replacement for tenofovir disoproxil and entecavir in HIV treatment regimens.

Hepatitis C Treatments

6.35. The Committee noted that there is a submission before the Medicines Classification Council (MCC) to allow nurses who are experienced with Hepatitis C (HepC) treatment to prescribe glecaprevir with pibrentasvir (Maviret).

6.36. The Committee reviewed the available treatments for HepC infection and considered that glecaprevir with pibrentasvir remained the appropriate first line treatment in the majority of cases, with some exceptions.

6.37. The Committee identified two groups of people who could not be treated with glecaprevir with pibrentasvir and for whom there was currently no funded alternatives. Members reiterated their recommendations (from email correspondence earlier in 2022) pertaining to the management of each group as follows:

6.37.1. Individuals with decompensated cirrhosis from Hepatitis C. Currently, sofosbuvir with ledipasvir (Harvoni) is funded but is ineffective in people infected with HCV genotype

2 or 3 (approximately half all cases in New Zealand); and individuals with Hepatitis C infection who have experienced treatment failure with Maviret or previous first line treatments.

Recommendation

Individuals with decompensated cirrhosis from Hepatitis C

6.38. The Committee **recommended** that sofosbuvir with velpatasvir (Epclusa) plus ribavirin be funded instead of sofosbuvir with ledipasvir (Harvoni) for the treatment of individuals with decompensated cirrhosis. The Committee noted that sofosbuvir with velpatasvir (Epclusa) plus ribavirin is effective against all HCV genotypes and would remove the need for genotyping. The Committee noted that the total number of people in this group was very small, approximately 5-6 people per year, split between genotype 1 and genotype 3.

6.39. The Committee further noted that ribavirin with Epclusa for 12 weeks was also an appropriate treatment regime for these people and that significant cost savings to the health sector could be realised from it as this treatment regime prevented most people from progressive liver disease that would otherwise eventually require transplantation.

Individuals with Hepatitis C infection who have experienced treatment failure with Maviret or previous first line treatments.

6.40. The Committee noted that the estimated failure rate of Maviret treatment was less than 1% but that 20-40 people per year could require retreatment depending on the numbers receiving treatment for HepC. The Committee noted that retreatment is currently through an open labelled study being conducted at the New Zealand Liver Transplant Unit (NZLTU), Auckland City Hospital. To date, 65 people who have not cleared Hepatis C infection after receiving Direct Acting Antiviral (DAA) treatment (mainly Maviret) have received sofosbuvir plus glecaprevir with pibrentasvir (Maviret) for 16 weeks with all but one being cleared of infection.

6.41. The Committee **recommended** that a combination retreatment regime of sofosbuvir/velpatasvir/voxilaprevir (Vosevi) or sofosbuvir plus glecaprevir with pibrentasvir (Maviret) be funded for this group. The Committee noted that of the two options, Vosevi was simpler to administer in the community due to one single tablet per day and a shorter treatment period (12 vs 16 weeks). However, in Maviret failures, sofosbuvir plus Maviret was more effective and did not require addition of ribavirin. The Committee noted that sofosbuvir plus Maviret was the preferred treatment option for these reasons.

Discussion

6.42. The Committee noted that the manufacturer of Ibavyr (ribavirin 200mg tablets) has indicated they intend to discontinue production in the future. The Committee noted that glecaprevir with pibrentasvir was not suitable for treating people with liver failure due to containing a protease inhibitor and that while alternative treatments existed, including ledipasvir/sofosbuvir (Harvoni) and sofosbuvir/velpatasvir (Epclusa), that the alternatives had significantly longer treatment periods and lower efficacy.

6.43. The Committee considered that the preferred treatment for people with HepC infection and liver failure was Epclusa plus ribavirin for 12 weeks. Members noted that ribavirin was also used for treatment of other viral infections including those with

epidemic potential such as measles, which could potentially require access to larger stocks than usual use.

6.44. The Committee noted that at present ribavirin was not listed on the HML and that access was via a special programme run by Pharmac. The Committee considered that HML listing was preferable to a special access pathway.

6.45. The Committee considered that access to ribavirin stocks should be secured and that there was a high need to maintain continuity of supply for this medicine for treatment of both Hepatitis C and other viral infections.

7. NPPA Application review

7.1. The Committee reviewed data provided by Pharmac on applications in the Anti-infectives Therapeutic Group via the NPPA process from the August 2020 – July 2022 period.

7.2. The Committee noted a number of paediatric applications for valganciclovir for congenital cytomegalovirus (CMV) infection and considered that it would be more appropriate to be available via Special Authority.

7.3. The Committee noted a number of applications for pristinamycin for antibiotic resistant Mycoplasma genitalium and that there was a notable amount of regional variation in use. Members considered that this was potentially due to different antibiotic guidelines between regions, with some regions using combination therapy of doxycycline and moxifloxacin. The Committee noted that it would be appropriate to consult sexual health physicians from those regions with higher use of pristinamycin to better understand prescribing patterns. Members noted they would like to review the use of pristinamycin at the next meeting.

7.4. The Committee noted a small amount of cefiderocol use and considered that it would be appropriate to investigate listing of cefiderocol on the HML for use in salvage therapy of susceptible infections. Members noted there was likely wider use of cefiderocol via hospital rapid assessments that were not included in this data.

8. Anti-Microbial Stewardship (AMS) Discussion

Record

8.1. The Committee noted that discussions around Anti-microbial Stewardship were limited due to the time available at the Committee meeting and that further discussion around the role of Pharmac in AMS would be valuable.

8.2. The Committee reviewed the Kotahitanga: Uniting Aotearoa against infectious disease and antimicrobial resistance report from the Prime Minister's Chief Science Advisor and noted the following AMS action points from the report as being specifically relevant to Pharmac:

8.3. Monitor and report transparently the quantity of antimicrobials used throughout the health sector.

8.4. Review Pharmac antimicrobial restrictions in the community and ensure they align with hospital restrictions and AMS principles.

8.5. Prioritise AMS under Pharmac's Factors for Consideration, including actively seeking to fund pharmaceuticals that align with AMS principles. This may involve

subsidising antimicrobials that facilitate oral management of infections in the community in line with AMS principles.

8.6. Establish a transparent national supply of rarely used antimicrobials for treating infections due to multidrug-resistant organisms in a timely manner, accessible across New Zealand.

8.7. Seek advice on and enable alternatives to antibiotics to be sought for appropriate conditions. As part of this the Committee considered funding of topical benzoyl peroxide as an alternative to oral antibiotics for acne, noting that it had been previously recommended by the Dermatology Advisory Committee and included in the Pharmac Annual Tender, but no product was currently listed. The Committee noted that due to the prevalence of acne that funded use of topical benzoyl peroxide could potentially be widespread. The Committee also considered that funding topical benzyl periodide would have positive equity and AMS implications as currently people typically progressed directly to either non-funded alternatives (which are relatively expensive) or funded doxycycline, with negative AMS implications. The Committee considered that Pharmac should attempt to source topical benzoyl peroxide and consider it for funding.

8.8. The Committee further noted that low-dose doxycycline was not funded for the treatment of acne and that this was another potential treatment due to the sub-antimicrobial dose of doxycycline used. Current funded doxycycline usage for acne and rosacea involved the higher strength 100mg tablet. The Committee noted that the published clinical evidence for use of low dose doxycycline involved relatively low numbers of individuals but considered that a lower dose tablet should be sought. The Committee considered that the majority of doxycycline usage in the 12-20 year age group would be for this indication and that the market size could be identified by this usage.

8.9. The Committee considered the report's recommendation that a measuring device be funded and dispensed alongside liquid medicines to promote appropriate antimicrobial dosing. The Committee noted that the primary benefit of providing a measuring device with liquid medicines would be to promote equity, safety and appropriate use of medicines. The Committee was supportive of the provision of a measuring device with community dispensing of all liquid medicines, but did not consider this would significantly impact antimicrobial resistance.

8.10. The Committee considered the report's recommendation regarding removing inconsistencies between community and hospital antimicrobial prescribing restrictions. The Committee noted a number of pharmaceuticals with inconsistencies between the community schedule and the hospital medicines list (HML).

8.11. The Committee noted for example, that ciprofloxacin in the community schedule has a recommendation for use for specific indications but no restriction, whereas the HML listing of ciprofloxacin is restricted to specific practitioners or protocols.

8.12. The Committee considered that ciprofloxacin community use should be an endorsed medication for the already named specific conditions and that usage should be restricted to second line use unless no other first line agent was appropriate.

8.13. The Committee also noted that norfloxacin in the community schedule is restricted to uncomplicated urinary tract infections (UTI's), while there is no hospital use restriction. The Committee considered that restrictions on hospital usage should be in-line with the restrictions placed on ciprofloxacin.

8.14. The Committee noted the following other antibiotics have differing community/hospital restrictions requiring further investigation:

- Fluconazole
- Fosfomycin
- Clindamycin
- Pyrimethamine sulfadiazine (used on discharge from hospital)

8.15. The Committee noted that it was important for Pharmac's funding restrictions to align with in-use treatment guidelines. Members noted that at present the lack of a single national guidelines made this difficult to maintain. The Committee noted that at present there was no single entity responsible for setting national antibiotic guidelines.

8.16. The Committee noted the Chief Science Advisor's report recommendation that amoxicillin with clavulanic acid community dispensing should be reduced via feedback to prescribers, or through restrictions on use. Members considered that at present usage of amoxicillin with clavulanic acid in the community was higher than expected. The Committee further noted that indication usage data was not available in relation to this dispensing so it was difficult to understand exactly what was driving the high levels of usage.

8.17. The Committee noted that while amoxicillin with clavulanic acid is preferred for a number of specific indications, from an AMR perspective the use of amoxicillin alone is the preferred alternative in many cases. The Committee considered that it would be appropriate to restrict amoxicillin with clavulanic acid to specific conditions, via endorsement or special authority, specifically:

- Pyelonephritis
- Diverticulitis
- Animal bites
- Cellulitis

8.18. The Committee further noted that an exception for paediatric use may be necessary for the oral liquid formulation as there are more limited alternatives for children who require oral liquids and that macrolides were also not preferred due to the generation of pneumococcal resistance.

8.19. The Committee noted its previous recommendation to amend restrictions for azithromycin by replacing current restrictions of five days azithromycin treatment for any indication, to that for certified conditions only. The indications include:

- Treatment of: Chlamydia, Mycoplasma genitalium, Legionella pneumonia, Pertussis for all age groups.
- Prophylaxis of: pertussis in pregnant or breastfeeding contacts of pertussis cases and Mycoplasma genitalium. Prophylaxis of diphtheria contacts.

The Committee considered that the previous recommendation was still appropriate due to the AMR risk as azithromycin was a long-acting macrolide which was currently not restricted to specific uses.

8.20. The Committee noted that there is no data around the use of Practitioner Supply Order (PSO) antimicrobials and that the list of antimicrobials available on PSO should be reviewed within an AMR framework. The Committee further considered that while the PSO usage of a pharmaceutical might be a low fraction of its overall usage, there was likely to be higher use for those living in rural areas, those with higher health need [requiring urgent care] or those facing financial or other barriers to dispensing of prescriptions. The Committee considered that not having visibility of antibiotic usage in these groups was a concern from an equity perspective. The Committee noted that Pharmac had considered these issues previously but that more analysis and information would be beneficial to creation of an informed response.

8.21. The Committee considered that probenecid would be appropriate to add to the PSO list as it was part of the recommended treatment regime for cellulitis in primary care. The Committee further considered that gentamicin for pyelonephritis should be added to PSO.

8.22. The Committee considered a number of antimicrobials are provided by Pharmacists as 'Pharmacist only' medicines. Specifically, trimethoprim and potentially nitrofurantoin for urinary tract infections. The Committee noted that at the present time such prescriptions are not funded and no centralised data is recorded around their dispensing. The Committee noted that were Pharmac to fund the cost of pharmaceuticals dispensed in this manner it would have visibility on dispensing numbers. The Committee considered that Pharmac should fund the cost of antimicrobials dispensed this way in order to gather data on usage for AMS purposes. Additionally, the Committee noted that for inexpensive medicines the majority of the cost of receiving a prescription in this manner was the pharmacist consult fee which would not be funded and recommended that Pharmac explore ways to reduce the cost to the individual.

9. Dolutegravir/lamivudine (DTG/3TC) for the treatment of Human Immunodeficiency Virus (HIV-1) infection in adults and adolescents (>12 years), who have no known or suspected resistance to either antiretroviral component

Application

9.1. The Committee reviewed the application from GlaxoSmithKline NZ Ltd for the use of dolutegravir/lamivudine (DTG/3TC) (Dovato) single tablet regimen for the treatment of HIV-1 infection in adults and adolescents (>12 years), who have no known or suspected resistance to either antiretroviral component.

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

Recommendation

9.3. The Committee **recommended** that dolutegravir/lamivudine (DTG/3TC) (Dovato) single tablet regimen be listed **only if cost-neutral** to the expected expenditure on HIV treatment regimens that Dovato would replace, within the context of treatments for infections, subject to the current Special Authority criteria for antiretrovirals (SA2139).

9.4. In making this recommendation, the Committee considered that:

- DTG/3TC would be convenient and appealing to many patients with HIV currently receiving multi-tablet combination treatment regimens.
- There is evidence that DTG/3TC is non-inferior to currently funded treatment regimens and would not offer any additional health benefits to patients with HIV, their family/whānau or to wider society above those associated with currently funded treatment options and formulations.

Discussion

Māori Impact Statement

9.5. The Committee considered that the impact of HIV on Māori health outcomes is similar to the impact it has on all people living with HIV, although acknowledged that Māori with HIV may experience additional challenges and barriers to healthcare access.

Health Need

9.6. The Committee considered that the health need of people living with HIV in New Zealand has not significantly changed since last discussed by the Anti-Infective Subcommittee in September 2020. The Committee noted the two components of DTG/3TC, dolutegravir (DTG) and lamivudine, are already funded and widely used, with DTG used by more than half of all people living with HIV in New Zealand. The Committee considered there was no unmet health need for this patient group.

9.7. The Committee considered that the impact of HIV on Māori health outcomes is similar to the impact it has on all people living with HIV, although acknowledged that Māori with HIV may experience additional challenges accessing healthcare at all levels, such as barriers relating to testing for diagnosis.

9.8. The Committee noted that international guidelines and clinical trial data support dual antiretroviral treatment either commencing with, or switching between, dolutegravir and lamivudine (DTG/3TC) or dolutegravir and emtricitabine (DTG/FTC). The Committee noted that these components are currently funded as either a two-pill or three-pill once a day regimen and considered these combination regimens are suitable for patients with HIV RNA <500,000 copies/mL and without chronic hepatitis B (HBV) coinfection. Members considered that about 3% of people living with HIV in New Zealand will also have chronic hepatitis B infection and were made aware of evidence from an observational study reporting that up to 5% of people newly diagnosed with HIV infection in New Zealand will have acquired HIV infection with transmitted resistance to nucleoside reverse transcriptase inhibitors (NRTIs) and/or integrase strand transfer inhibitors (INSTIs) (Young et al. Intern Med J. 2020;50:872-6).

Health Benefits

9.9. The Committee noted that DTG/3TC (Dovato) contains dolutegravir 50mg + lamivudine 300mg and is an ongoing treatment administered as one oral tablet once daily. The Committee noted that the key evidence for this application comes from four large clinical trials and that the use of the DTG/3TC regimen is already established in international treatment guidelines.

9.10. The Committee noted that the GEMINI-1 and GEMINI-2 trials are identical, multicentre, phase III, randomised (1:1), double-blind, non-inferiority studies

conducted at 192 centres in 21 countries. The trials included a total of 1,441 treatment-naive adults across both studies with HIV-1, HIV-1 RNA ≤500,000 copies/mL and no major viral resistance mutations to NRTIs, non-nucleoside reverse transcriptase inhibitors, or protease inhibitors. Participants received once daily DTG/3TC or once daily DTG + tenofovir disoproxil fumarate/emtricitabine (TDF/FTC).

9.11. The Committee noted that, at week 144, DTG/3TC was non-inferior to DTG + TDF/FTC in proportion of participants achieving HIV-1 RNA <50 copies in the pooled analysis (82% vs 84%, respectively; adjusted treatment difference [95% CI], −1.8% [−5.8, 2.1]), GEMINI-1 (−3.6% [−9.4, 2.1]), and GEMINI-2 (0.0% [−5.3, 5.3]) (Cahn et al. AIDS. 2022;3:39-48). The Committee also noted results from these studies which were published after 48-week and 96-week data cut-offs (Cahn et al. Lancet. 2019;393:143-55; Cahn et al. J Acquir Immune Defic Syndr. 2020;83:310-18). The Committee considered that the trial results indicated non-inferiority of the two-drug regimen compared with the three-drug regimen.

9.12. The Committee noted that TANGO was a multicentre, open-label phase III, non-inferiority randomised (1:1) controlled trial of 743 adults with HIV-1 RNA <50 copies/mL on a 3- or 4-drug tenofovir alafenamide (TAF)-based regimen who switched to once-daily fixed-dose DTG/3TC or remained on a 3 or 4 drug TAF–based regimen. The Committee noted that the application included a publication reporting data up to week 48 (Van Wyk et al. Clin Infect Dis. 2020;71:1920-9) and a 2021 conference poster by Osiyemi et al. The Committee was made aware of a recent publication reporting non-inferiority of switching to DTG/3TC compared with continuing TAF-based regimens (adjusted difference in proportion of participants with HIV RNA ≥50 copies/mL, −1.1%; 95% CI, −2.4% to 0.2%) at 144 weeks (Osiyemi et al. Clin Infect Dis. 2022;75:975-86).

9.13. The Committee noted that SALSA was a randomised (1:1), controlled, open label study of 493 adults with HIV-1 RNA <50 copies/mL for >6 months on a three-drug or four-drug regimen without prior virological failure or NRTI or DTG resistance-associated mutations (Llibre et al. J Int AIDS Soc. 2021;24:Suppl_4). Participants switched to the two-drug regimen DTG/3TC FDC or continued any current three- or four-drug antiretroviral regimen (CAR). The target sample size was 600, however, this was reduced to 490 due to the COVID-19 pandemic. The Committee noted that the most recently published data reported that 1/222 (0.5%) in the DTG/3TC group and 3/234 (1.3%) in the current anti-retroviral (CAR) group had HIV-1 RNA ≥50 c/mL at week 48 (adjusted difference, −0.8%; 95% CI, −2.5% to 0.9%), demonstrating non-inferiority (Llibre et al. Clin Infect Dis. 2022;ciac130. Online ahead of print).

9.14. The Committee noted a Pharmac-identified publication from a randomised, open-label, non-inferiority study reporting three-month adherence of 209 participants in China to either a three-tablet or a two-tablet Efavirenz-based regimen (Xiao et al. Int J Infect Dis. 2022;117:48-55). The authors reported no significant difference of adherence between the two treatment groups, as analysed using self-reported adherence questionnaires. The Committee noted two studies (Hodder S et al. AIDS Patient Care STDS; 24; 2010), (M. Airoldi,et al; Patient Prefer Adherence; 4; 2010) which supported improved adherence and treatment satisfaction with a single pill treatment regimen but considered that the overall quality of life impact was small and there was a lack of non-adult data. Members also noted the potential for differential tablet adherence (where a patient takes only part of their daily multi-pill regimen) with multi-tablet regimens which was eliminated by a single tablet regimen.

9.15. The Committee considered that the evidence supports non-inferiority of DTG/3TC to currently funded HIV treatment regimens and therefore the single tablet of DTG/3TC would provide the same health benefit and risks as the individual funded medicines used in combination. The Committee considered that DTG/3TC would not be expected to significantly improve adherence, produce a health benefit for family, whānau or wider society, or lead to any other consequences to the health system.

Suitability

9.16. The Committee considered that most clinicians in New Zealand would be happy to offer treatment with DTG/3TC, if funded, and to change those eligible to this from their current treatment as it would be consistent with the HIV treatment paradigm. The Committee considered that many of those who are eligible could switch to DTG/3TC with ease, although acknowledged there may be some reluctance to switch treatment of patients who are currently stable on treatment.

9.17. The Committee considered that, if DTG/3TC were funded, there would not be any clinical reasons to prevent people from switching back from combination to non-combination pill regimens of dolutegravir and lamivudine in the future (eg if dolutegravir was available in a generic version). However, the Committee noted that some individuals could be inconvenienced or concerned by a change from a single tablet regimen back to a two-tablet regimen. Members were made aware of evidence of the high acceptance of such a change in the Netherlands and France where this had been discussed beforehand with people living with HIV (Engelhard et al. Drugs Real World Outcomes; 2016; 2;3(2):223-230) , and considered that a similar approach to implementation in New Zealand could be beneficial if such a change were necessary (eg for fiscal reasons).

Costs and savings

9.18. In summary, the Committee noted the two components of DTG/3TC were already funded, acknowledged the appeal of a single pill regimen and the possible reluctance to switch treatment of individuals whose condition was stable, and considered that there was no unmet health need for this treatment. The Committee recommended DTG/3TC be funded only if cost-neutral to the weighted average of current HIV combination treatment regimens.

9.19. The Committee noted the supplier proposed that, if DTG/3TC were to be funded, clinical management would be expected to change in the following ways:

- Initiation of an INSTI-based regimen for treatment naïve patients would use DTG/3TC.
- For those already on treatment, but unable to tolerate current treatment and requiring an INSTI, DTG/3TC would be considered.

9.20. The Committee considered that almost all treatment-naïve patients would likely commence on a three-drug regimen (predominantly emtricitabine with tenofovir disoproxil and dolutegravir, FTC/TDF+DTG) and subsequently about 90% of these would be expected to switch to a two-drug regimen of DTG/3TC if treatment naïve resistance testing did not demonstrate resistance and in the absence of chronic hepatitis B infection. The Committee considered that treatment naïve patients suitable for DTG/3TC would have a viral load of <500,000 copies/mL based on the concern that a high viral load may be hard to suppress with a two-drug regimen, and should not have chronic hepatitis B coinfection, as tenofovir would be required to manage this.

9.21. The Committee considered that the supplier's expectation for those already on treatment did not represent what would likely occur in the New Zealand context and considered that significant numbers would change to DTC/3TC, if funded, due to the appeal of a new, novel, single-tablet treatment. The Committee considered that the majority of those who would switch to DTG/3TC would be those individuals who are stable on a three-drug regimen, although some people would also switch due to tolerability issues on their current treatment.

9.22. The Committee considered that most people would already be receiving the combination regimen and that the key differences with the proposed treatment were removing tenofovir and reducing the number of pills to be taken per day.

9.23. The Committee considered that there would be very high interest and enthusiasm for a novel, single-tablet regimen such as DTG/3TC, if funded, from people living with HIV, non-government organisations and relevant clinicians. The Committee considered that 64% of existing people would be eligible to change and up to 86% of eligible people could decide to change (estimates based on the review of a clinic containing 299 adult people living with HIV). Based on these estimates, the Committee considered this would result in significant uptake of approximately 55% of the eligible group, predominantly those currently receiving antiretroviral therapy for HIV, equal to approximately 1,650 people within the first two years of funding. The Committee considered that 90% of people newly diagnosed would also be initiated on DTG/3TC. The Committee therefore considered that the number of individuals who would receive DTG/3TC would be greater than those estimated by the supplier (287 in year one and 902 in year five). Members considered that it was more likely that estimates would be approximately 885 people in year one (60 who are newly diagnosed and 825 people already on treatment) and approximately 1,950 people in year five (300 who are newly diagnosed plus 1,650 people already on treatment).

Special Authority Criteria

9.24. The Committee considered it reasonable for DTG/3TC, if funded, to be subject to the current Special Authority criteria for antiretrovirals (SA2139), requiring confirmed HIV infection for initial applications. The Committee noted that the current initial approvals appropriately allow for lifelong treatment therefore renewal would not be required and that DTG/3TC tablets would be counted as two antiretroviral therapies for the purposes of the Special Authority.

Summary for Assessment

9.25. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for DTG/3TC if it were to be funded in New Zealand for people >12 years of age with HIV-1 infection who have no known or suspected resistance to either antiretroviral component. 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 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 (>12 years) with HIV-1 infection who have no known or suspected resistance to either antiretroviral component. Treatment naïve individuals with viral load of <500,000 copies/mL and no HBV coinfection. Treatment experienced individuals with a suppressed HIV viral load and no HBV coinfection.
Intervention	One tablet once daily (dolutegravir 50mg + lamivudine 300mg), as ongoing treatment.
Comparator(s)	Three/four drug HIV regimens. Most common regimens likely to be: • Emtricitabine with tenofovir disoproxil (FTC/TDF) + dolutegravir (DTG) • Abacavir sulphate with lamivudine (ABC/3TC) + dolutegravir (DTG) • Emtricitabine (FTC) + dolutegravir (DTG)
Outcome(s)	Non-inferior efficacy compared to three/four drug antiretroviral regimens.

Table definitions:

Population: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup)

Intervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).

Comparator: Details the therapy(s) that the target population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).

Outcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.