Transparency, Reforms and Evaluation Support Section
Prescription Medicines Authorisation Branch
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606

31 March 2019

Dear Sir/Madam,

Consultation: Proposed criteria for Appendix M of the Poisons Standard to support rescheduling of substances from Schedule 4 (Prescription only) to Schedule 3 (Pharmacist only)

Purpose

The New South Wales Antimicrobial Stewardship Pharmacist Network (NASPN) makes this submission to the Therapeutic Goods Administration (TGA) on the consultation on *Proposed criteria for Appendix M of the Poisons Standard to support rescheduling of substances from Schedule 4 (Prescription only) to Schedule 3 (Pharmacist only)*.

It is understood that medications for potential consideration of down-scheduling from Schedule 4 to Schedule 3 have been identified to facilitate better access to medicines and support appropriate self care. It is noted that systemic antimicrobials including trimethoprim, nitrofurantoin and others were considered and identified as a high priority. **NASPN strongly opposes the down-scheduling of trimethoprim, and any other antimicrobial agents that are being considered.**

About NASPN

NASPN is a collaborative network of sixty-four specialist and senior specialist antimicrobial stewardship (AMS) and infectious diseases (ID) pharmacists employed within health care systems and organisations in New South Wales and the Australian Capital Territory. NASPN members have a key focus on ensuring optimal outcomes for patients, and all people, through the appropriate utilisation of antimicrobial agents.

Summary of NASPN's recommendations

NASPN strongly opposes the down-scheduling of trimethoprim, or any systemic or topical antimicrobials, from Schedule 4 to Schedule 3. We believe the proposition will drive increasing rates of trimethoprim resistance in the community and lead to potential patient harm through misdiagnosis of severe and resistant urinary tract infections. As proposed, the down-scheduling of trimethoprim from Schedule 4 to Schedule 3 is against the fundamental principles of antimicrobial stewardship, and contradicts the holistic approach required for antimicrobial prescribing as highlighted by the Australian Commission on Safety and Quality in Health Care (ACSQHC), in the Antimicrobial Stewardship Clinical Care Standard.

There are major scientific hurdles impeding the discovery and development of novel antimicrobial agents. As such, NASPN is of the opinion that future TGA proposals to reschedule antimicrobials should strengthen rather than weaken protections, by promoting judicious antimicrobial use, in order to prolong the life/usability of antimicrobials in our armamentarium. The threat of antimicrobial resistance should be at the frontier of prescribing considerations and thus we suggest that any further considerations should involve intensive consultation with infectious diseases and microbiology professional bodies, colleges and advisory groups.

The specific issues highlighted represent the professional, expert opinions of the authors and members of NASPN, and are not made as a representation of the health services in which they are employed.

Comments on specific issues

1. Antimicrobial resistance

Antimicrobial resistance (AMR) has recently been listed as one of the top 10 threats to global health[1], requiring urgent coordinated and multisectoral action. Given antimicrobial misuse and overuse is the principal driver of AMR, much attention has duly been placed on strengthening regulatory control over antimicrobial use, as well as improving antimicrobial prescribing and stewardship efforts in both the human and animal health sectors.

There is strong political will to reduce the emergence and spread of AMR as a means of improving patient care and strengthening regional and global health security, as evidenced by the early development of the National AMR Strategy 2015-2019. In particular, priority area 2.5 of the strategy commits to *"strengthen existing measures to better support appropriate and judicious use"* of antimicrobials, including the implementation of regulations to govern access to antimicrobials to avoid inappropriate use[2].

Down-scheduling of trimethoprim from Schedule 4 to Schedule 3 will invariably lead to increased access and use, with subsequent increased rates of resistance and the threat of trimethoprim becoming ineffective. This has been demonstrated in New Zealand, where trimethoprim became available from trained pharmacists in 2012. Usage of trimethoprim was shown to increase from 2011 to 2014[3], and New Zealand now has the highest rate of trimethoprim use in the region[4]. Resistance of urinary *Escherichia coli (E. coli)* to trimethoprim increased accordingly from 24.4% in 2011[5] to 26.1% in 2015[6].

Australia already has significant and increasing rates of trimethoprim resistance in *E. coli*, increasing from 21-29% in 2014[7] to 33% in 2017[8]. Down-scheduling of trimethoprim will only drive this further and increase the risk of treatment failure and progression of UTI to urinary sepsis. Similar proposals for down-scheduling of trimethoprim have previously been withdrawn in the United Kingdom due to concerns for increasing AMR[9].

[1] World Health Organization (WHO) 2019, Ten threats to global health in 2019, viewed 16 March 2019, https://www.who.int/emergencies/ten-threats-to-global-health-in-2019

[2] Australian Government 2015, Responding to the threat of antimicrobial resistance: Australia's First National Antimicrobial Resistance Strategy 2015-2019, Commonwealth of Australia, Canberra.

[3] Williamson, DA, Roos, RF & Verrall, A 2016, Antibiotic consumption in New Zealand, 2006-2014, The Institute of Environmental Science and Research Ltd, Porirua.

[4] The Centre for Disease Dynamics Economics & Policy 2018, ResistanceMap: Use of trimethoprim in 2015, viewed 16 March 2019, https://resistancemap.cddep.org/AntibioticUse.php

[5] The Institute of Environmental Science and Research Ltd 2011, viewed 16 March 2019, https://surv.esr.cri.nz/PDF_surveillance/Antimicrobial/AR/National_AR_2011.pdf

[6] The Institute of Environmental Science and Research Ltd 2015, viewed 16 March 2019, https://surv.esr.cri.nz/PDF_surveillance/Antimicrobial/AR/National_AR_2015.pdf

[7] Australian Commission on Safety and Quality in Health Care (ACSQHC) 2017, AURA 2017: second Australian report on antimicrobial use and resistance in human health, ACSQHC, Sydney.

[8] Australian Group on Antimicrobial Resistance (AGAR) forthcoming 2019, Sepsis Outcomes Programs: 2017 Report, AGAR, Sydney.

[9] Andalo, D 2010, How a POM-to-P culture change may be thwarting pharmacists' ambitions, *The Pharmaceutical Journal*, vol. 284, pp. 445.

2. Urinary tract infection (UTI) diagnostics

Appropriate antimicrobial prescribing and the effective treatment of UTIs is contingent on the collection and assessment of urine cultures before the first dose of an antimicrobial. The Therapeutic Guidelines: Antibiotic[1], which are the national guidelines for antimicrobial prescribing in Australia, clearly state that the diagnosis of a UTI is based **not** only on the presence of symptoms, but a significant concentration of uropathogenic bacteria in the urine. This can only be done by obtaining a urine culture before antimicrobials are administered.

There is a significant gap in current pharmacists' capacity to diagnose a UTI as they lack appropriate equipment to obtain a viable urine culture, and do not have access to, or sufficient training to interpret, the subsequent pathology results. The consequence of trimethoprim treatment that is not guided by microbiology identification and susceptibility will be the inappropriate and ineffective treatment of UTIs where the bacteria causing the infection is resistant to trimethoprim. The 2019 Australian Group on Antimicrobial Resistance (AGAR) Sepsis Outcome Program Report[2] has indicated that over 30% of *E. coli,* which causes up to 95% of UTIs, is resistant to trimethoprim. Ultimately, this shows there is an unacceptably high risk of treatment failures for trimethoprim if it were to be down-scheduled from Schedule 4 to Schedule 3 in the addition of Appendix M.

Treatment failures have been investigated in the primary care setting where the attributable cause is antimicrobial resistance; the problem is further perpetuated when one in seven patients given an antimicrobial (usually trimethoprim) for UTI symptoms will return within 28 days for another course[3,4]. The diagnosis of UTIs based purely on symptoms is controversial[1,5,6].

Pharmacists in Australia are not currently qualified to diagnose UTIs utilising the appropriate history, physical examination and investigations of the patient. There is an inherent risk of pharmacists missing a differential diagnosis (e.g. vaginitis, interstitial cystitis or chlamydia urethritis) or complications of a UTI (e.g. prostatitis, pyelonephritis or peri-renal abscess). The most important complication that bears significant mortality is sepsis. The mortality rate ranges from 20-40% in sepsis from a urinary tract source[7]. In addition to this, the associated mortality increases significantly with age[8], which is very relevant in this discussion considering the aging Australian population.

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[1] Antibiotic Expert Group, Therapeutic Guidelines Limited. Therapeutic Guidelines : Antibiotic. 15, 2014. ed2014.Urinary Tract Infections p417.

[2] Australian Group on Antimicrobial Resistance (AGAR) forthcoming 2019, Sepsis Outcomes Programs: 2017 Report, AGAR, Sydney.

[3] Lawrenson RA, Logie JW. Antibiotic failure in the treatment of urinary tract infections in young women. Journal of Antimicrobial Chemotherapy. 2001;48(6):895-901.

[4] PHE. English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) Report 2018. Public Health England, 2018: 147.

[5] Goettsch WG, Janknegt R, Herings RM. Increased treatment failure after 3-days' courses of nitrofurantoin and trimethoprim for urinary tract infections in women: a population-based retrospective cohort study using the PHARMO database. British journal of clinical pharmacology. 2004;58(2):184-9.

[6] Ferry S, Burman LG, Holm SE. Clinical and bacteriological effects of therapy of urinary tract infection in primary health care: relation to in vitro sensitivity testing. Scand J Infect Dis. 1988;20(5):535-44.

[7] Gharbi M, Drysdale JH, Lishman H, Goudie R, Molokhia M, Johnson AP, et al. Antibiotic management of urinary tract infection in elderly patients in primary care and its association with bloodstream infections and all cause mortality: population based cohort study. BMJ. 2019;364:l525.

[8] Wagenlehner FM, Lichtenstern C, Rolfes C, et al. Diagnosis and management for urosepsis. Int J Urol 2013;20:963-70.

3. Antimicrobial surveillance and monitoring

Effective surveillance and monitoring of antimicrobial use is a key measure advocated worldwide in response to AMR. It is one of the five strategic priorities of the World Health Organisation's Global Action Plan on AMR[1], and one of the seven key objectives of the National AMR Strategy 2015-2019[2]. The consultation paper for the proposed down-scheduling of substances from Schedule 4 to Schedule 3 states that *"it is not expected that systems for real-time data collection and sharing would typically be required for S3, Appendix M goods."* As presented, the expectations for record keeping and reporting for Appendix M substances do not comply with national and international expectations of antimicrobial surveillance, and threaten the validity and reliability of the Antimicrobial Use and Resistance in Australia (AURA) program.

The second Australian report on antimicrobial use and resistance in human health (AURA 2017)[3] highlighted that antimicrobial dispensing rates in the Australian community are substantially higher than in benchmark countries that have comparable systems and levels of health care, including Sweden, Denmark, Norway, the Netherlands, England, Scotland and Canada. Weakening protection and restriction of antimicrobial agents through down-scheduling from Schedule 4 to Schedule 3 opposes the measures recommended by the ACSQHC to broaden and intensify efforts to reduce inappropriate antimicrobial use in the community.

Allowing pharmacists to prescribe antimicrobial agents, without the expectation for reporting and surveillance, may inevitably contribute to increased antimicrobial use in the community confounded by the inability to effectively monitor the increased use.

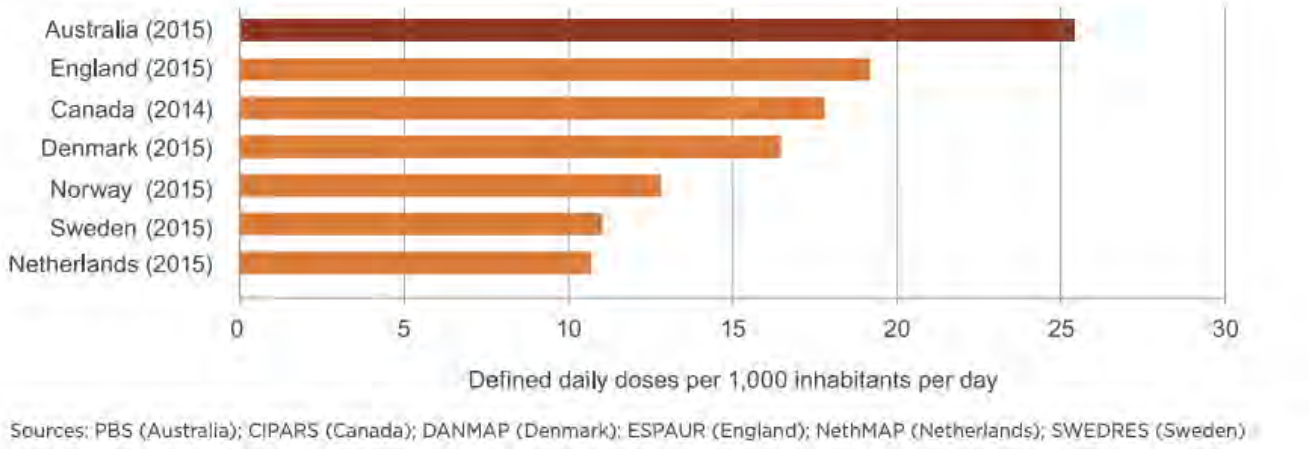

Fig 1: Comparison of community antimicrobial use in Australia and other similar countries, DDD/1000 inhabitants per day. Source of diagram: AURA 2017: Second Australian report on antimicrobial use and resistance in human health[2]

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[1] Global action plan on antimicrobial resistance. Geneva: World Health Organization; 2015. Available from: http://apps.who.int/iris/bitstream/10665/193736/1/9789241509763_eng.pdf

[2] Australian Government 2015, Responding to the threat of antimicrobial resistance: Australia's First National Antimicrobial Resistance Strategy 2015-2019, Commonwealth of Australia, Canberra.

[3] Australian Commission on Safety and Quality in Health Care (ACSQHC). AURA 2017: second Australian report on antimicrobial use and resistance in human health. Sydney: ACSQHC; 2017.

4. Separation of prescribing and dispensing

While the expertise of pharmacists in health care is utilised in Australia more than ever, including through the prescribing of vital primary care medicines in Schedules 2 and 3 of the SUSMP and the prescribing and administration of vaccinations, the Western tradition of separating prescribing and dispensing is a fundamental ethical and clinical concept to secure patient safety.

Pharmacist dispensing of medicines ensures a final clinical check for inappropriate prescribing, contraindications, interactions and other considerations. NASPN believes that this separation must be maintained within the existing frameworks in which pharmacists practice in Australia.

Furthermore, down-scheduling of trimethoprim from Schedule 4 to Schedule 3 will create a fragmentation of care between pharmacists and medical practitioners. This is because the current proposal does not mandate the need for pharmacists to report antimicrobial prescribing to a patient's general practitioner or other doctors, creating suboptimal standards for follow up and review.

Concluding comments

The care of patients with infectious diseases such as urinary tract infections must occur in a holistic manner, utilising available diagnostics tools, clinical expertise and experience, principles of antimicrobial stewardship and with comprehensive surveillance and monitoring. NASPN believes all systemic antimicrobial agents should remain in Schedule 4 of the SUSMP, prescribed by medical practitioners who are equipped with adequate knowledge and training to appropriately and safely prescribe antimicrobial agents. With regard to antimicrobials, pharmacists should continue to practice within their vital role as the final clinical check of prescriptions before treatment commences, a critical piece in the efforts of antimicrobial stewardship.

Australia currently performs significantly poorly in the volume of community antimicrobial use, driving increased and concerning rates of antimicrobial resistance. NASPN strongly recommends that the TGA reconsiders down-scheduling trimethoprim or any other antimicrobials from Schedule 4 to Schedule 3, in the interests of patient care and outcomes.

Yours sincerely,

The New South Wales Antimicrobial Stewardship Pharmacist Network

NASPN members acknowledge the Traditional Owners of country throughout Australia and recognise their continuing connection to land, waters and culture. We pay our respects to their Elders past, present and emerging.

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