Application for the reclassification of Trimethoprim to restrict supply to Prescription Medicine with no exceptions.

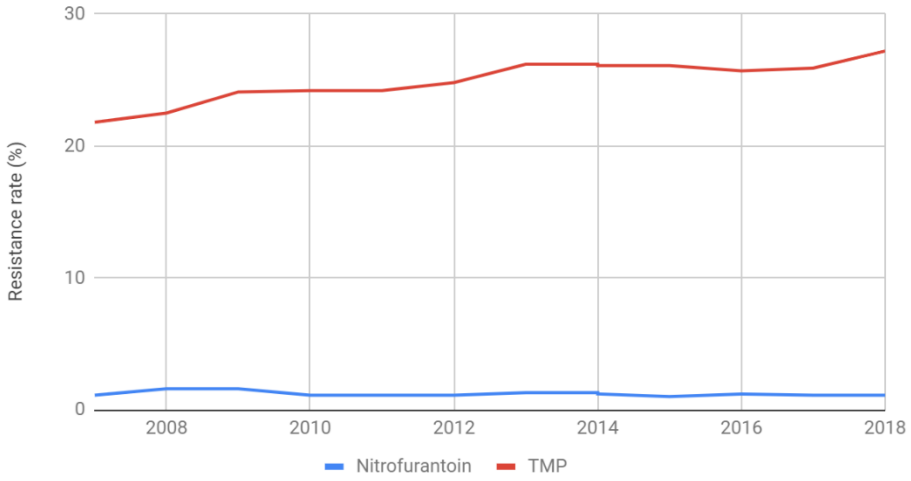
Executive Summary

On 12 July 2012, trimethoprim was reclassified from Prescription Medicine to Prescription Medicine; except in medicines for oral use containing 300 milligrams or less per dose unit when sold in a pack of 3 solid dosage units to a woman aged 16-65 years for the treatment of an uncomplicated urinary tract infection by a registered pharmacist who has successfully completed the New Zealand College of Pharmacists' training in the treatment of urinary tract infections by means of a notice in the New Zealand Gazette.

The Minutes for the 68th meeting of the Medicines Classification Committee 26 April 2022 note that the Committee would welcome submissions for consideration of the reclassification of trimethoprim.[1]

Since 2012, New Zealand community and hospital reported antibiotic resistant rates to trimethoprim have remained consistently well above the World Health Organisation recommended cut-off point for first line empiric treatment use of 20%. [2]

Figure 1. New Zealand *E.coli* resistance rate 2007-2018[3]



New Zealand, and international, uncomplicated urinary tract infection (UTI) treatment guidelines no longer recommend empiric trimethoprim and instead recommend empiric nitrofurantoin as the first line treatment. [4] [5] [6] Recently nitrofurantoin modified release capsules has been recommended for reclassification to allow Pharmacist supply in New Zealand. [7]

This is a submission for the reclassification of Trimethoprim to Prescription Medicine, with no exceptions.

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[1] Minutes of the 68th meeting of the Medicines Classification Committee - 26 April 2022
[2] Ikram R. 2013. Upfront: Antimicrobial Resistance in New Zealand: What is my role in primary care? Best Practice Journal New Zealand 54
[3] Antimicrobial susceptibility data from hospital and community laboratories, Institute of Environmental Science and Research Ltd, New Zealand, 2007-2018.
[4] European Association of Urology, Guidelines on Urological Infections, updated 2022.
[5] https://aucklandregion.communityhealthpathways.org/26703.htm
[6] https://bpac.org.nz/antibiotics/guide.aspx#uti-adult
[7] Classification of Medicines Gazette Notice, 25 October 2022.

Part A.

1. International Non-proprietary Name (or British Approved Name or US Adopted Name) of the medicine.

Name: Trimethoprim

2. Proprietary name(s).

TMP® and any subsequent trimethoprim proprietary names.

3. Name of the company / organisation / individual requesting a reclassification.

Te Arai BioFarma Limited

Auckland, New Zealand

4. Dose form(s) and strength(s) for which a change is sought.

300 mg tablets

5. Pack size and other qualifications.

300 mg x 3 tablets. The registered pack size for TMP® 300mg is 50 tablets.

This is a submission for the reclassification of trimethoprim from prescription medicine except when supplied in packs of three tablets to women aged 16 to 65 years for uncomplicated urinary tract infection by a pharmacist who has successfully completed the New Zealand College of Pharmacists' training in the treatment of urinary tract infections **to** prescription medicine.

6. Indications for which change is sought.

Trimethoprim tablets are indicated for the treatment of acute urinary tract infections.

7. Present classification of the medicine.

Prescription Medicine; except when supplied in packs of three tablets to women aged 16 to 65 years for uncomplicated urinary tract infection by a pharmacist who has successfully completed the New Zealand College of Pharmacists' training in the treatment of urinary tract infections.

8. Classification sought.

Prescription Medicine.

9. Classification status in other countries (especially Australia, UK, USA, Canada).

Australia – S4 Prescription Medicine.

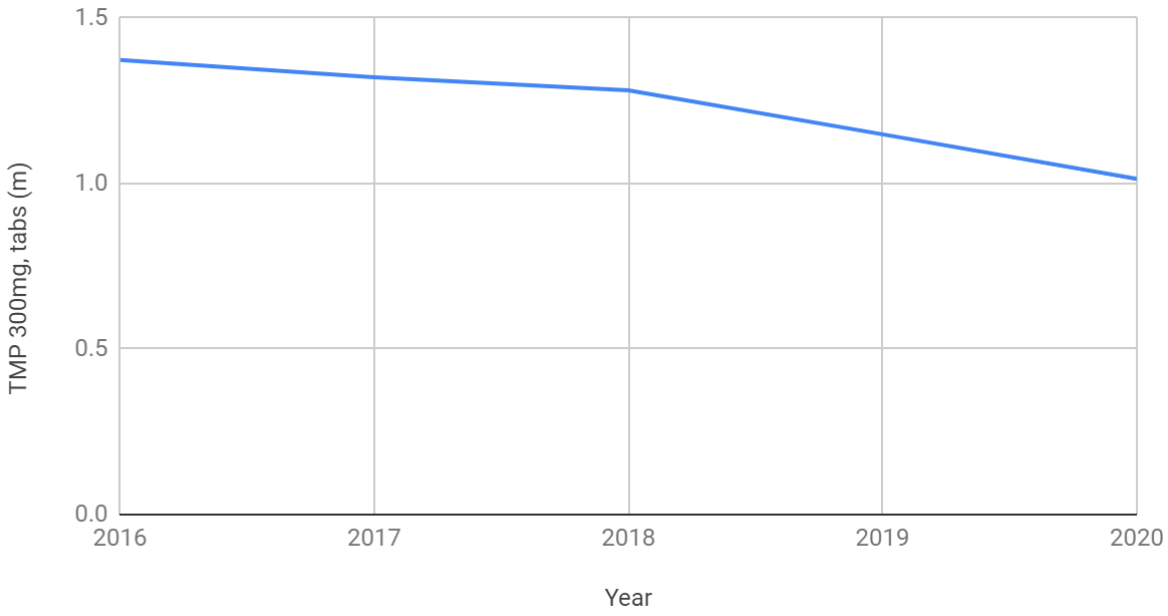
Canada – Pharmacist (according to defined inclusion and exclusion criteria)

UK - Trimethoprim is available under patient group direction (PGD) in the UK for urinary tract infection. A PGD allows certain specified health professionals (e.g. pharmacists) who have received training for that PGD to supply the medicine without prescription to patients according to specific criteria laid out in the PGD.

USA – Prescription Medicine.

10. Extent of usage in New Zealand and elsewhere (eg, sales volumes) and dates of original consent to distribute.

Figure 2. New Zealand TMP usage 2016-2020



TMP 300mg annual volume (tablets) as reported by Datapharm. Datapharm reports usage data of Pharmac funded, community medicines only. [8]

The original consent to distribute trimethoprim tablets in NZ was 3 December 1981.

[8] Pharmaceutical data webtool available at www.health.govt.nz

[9] Urinary tract infections (UTIs) – an overview of lower UTI management in adults, eBPJ 3, Nov 2021.

11. Local data or special considerations relating to New Zealand (if applicable)

In recent years New Zealand, as well as international guidelines, have been updated wherein modified release nitrofurantoin (Macrobid) 100 mg twice daily for 5 days is now the recommended first-line empiric treatment for non-pregnant women with acute, uncomplicated cystitis (UTI). [4-6] Trimethoprim (TMP) is no longer a first-line empiric choice owing to the high level of antibiotic resistance (>27%). [3]

The Best Practice Advisory Centre New Zealand provide the following rationale for trimethoprim no longer being a recommended first line treatment option –

"Previously, trimethoprim was considered a first-line empiric option for managing uncomplicated UTIs, and it has been commonly prescribed by clinicians in primary care. Since 2012, pharmacists who have completed a UTI training course have been able to supply trimethoprim without a prescription to females with a suspected UTI aged 16 – 65 years who are not pregnant and do not have any other complicating factors.

However, there is now evidence that trimethoprim should not be a first-choice antibiotic for managing uncomplicated lower UTIs due to a growing pattern of resistance across New Zealand. A multi-region audit of urine samples obtained between June 2016 and August 2018 demonstrated that approximately one-quarter of all E. coli isolates from females aged 15 – 55 years lacked trimethoprim sensitivity. In comparison, < 1% of E. coli tested were resistant to nitrofurantoin, and < 5% were resistant to cefalexin. Although trimethoprim is often preferred by people due to its once daily dosing, these findings suggest that nitrofurantoin and cefalexin are generally better empiric antibiotic treatment choices – unless there is recent community resistance data available to pragmatically guide such decisions."[9]

12. Labelling or draft labelling for the proposed new presentation(s).

N/A. No change to the current TMP label would be required.

13. Proposed warning statements if applicable.

N/A.

14. Other products containing the same active ingredient that would be affected by the proposed change.

TMP® tablets are the only brand of trimethoprim currently Medsafe registered. Other Medicines containing trimethoprim i.e. combination products would be unaffected by this change.

Part B.

1. Indications and dose

Trimethoprim 300 mg tablets are indicated for the treatment of acute urinary tract infections.

2. Presentation

The product for reclassification is trimethoprim in medicines for oral use containing 300 milligrams or less per dose unit.

3. Consumer benefits

New Zealand community and hospital TMP resistance rates are well in excess of the World Health Organisation recommendation of <20% for first line empiric antibiotic use. The use of trimethoprim in patients that have trimethoprim resistant isolates significantly reduces treatment efficacy. Subsequently the risk of continued UTI and progression to serious health outcomes including pyelonephritis, sepsis and the requirement for hospitalisation is increased. The ongoing use of antibiotics where resistant isolates are present increases the risk of resistant isolates proliferation within the community.

Recently Macrobid (nitrofurantoin modified release capsules) has been reclassified to allow Pharmacist supply.[7] The reclassification to restrict TMP to Prescription Medicine means that pharmacist supply for the treatment of UTI will be consistent with current guidelines. [4,5]

Efficacy of acute therapy with trimethoprim

Trimethoprim is no longer a first line empiric treatment for acute uncomplicated UTI. [4,5]

Antimicrobial Stewardship

New Zealand community and hospital TMP resistance rates are well in excess of the World Health Organisation recommendation of <20% for first line empiric antibiotic use. In contrast New Zealand resistance rates to nitrofurantoin are consistently around 1.0%. (ESR).

4. Contraindications and precautions

Contraindications and precautions were included in the 2012 submission. These are not relevant to this reclassification submission.

5. Undesirable effects, 6. Overdose, 7. Medication errors and abuse/misuse potential

Undesirable effects, overdose, medication errors and abuse/misuse potential information were included in the 2012 submission. These are not relevant to this reclassification submission.

8. Communal harm and / or benefit

Trimethoprim is no longer a first line treatment for acute uncomplicated UTI owing to the risks associated with antimicrobial resistance. The 2018 level of trimethoprim resistance was >27%.[3]

The use of trimethoprim in patients that have trimethoprim resistant isolates significantly reduces treatment efficacy. Subsequently the risk of continued UTI and progression to serious health outcomes including pyelonephritis, sepsis and the requirement for hospitalisation is increased. The ongoing use of antibiotics where resistant isolates are present increases the risk of resistant isolates proliferation within the community.

9. Integrated benefit-risk statement

The reclassification of TMP to Prescription Medicine benefits patients by:

- Helping to ensure that the guideline recommended first line empiric UTI treatment (nitrofurantoin modified release capsules) is supplied to patients from pharmacy.
- Reducing the risk of UTI treatment failures and the associated increased risk of serious health outcomes.
- Improving antimicrobial stewardship.

10. Risk mitigating strategies

The reclassification of TMP to Prescription Medicine is itself a risk mitigation strategy to:

- Reduce the risk of first line uncomplicated UTI treatment failures due to resistance, and
- Reduce the impact of TMP related antimicrobial resistance.