Classification of Trimethoprim

Information paper for the Medicines Classification Committee

Medsafe
January 2018

1. Purpose

The Chair of the Medicines Classification Committee (MCC) requested that Medsafe investigate the use of and resistance to trimethoprim following the reclassification in 2012 to prescription medicine; except when supplied in packs of three tablets to women aged 16 to 70 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. This information paper presents data collected by Medsafe from PHARMAC and ESR.

2. Background

At the 47th meeting of the MCC on 1 May 2012, Pharmacybrands Limited (the parent company for Life, Unichem, Amcal, Radius and Care Pharmacies in New Zealand) made a submission for the reclassification of trimethoprim. The submission proposed a reclassification from prescription medicine to prescription medicine except when supplied in packs of three tablets to women aged 16 to 70 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. The submission is attached in Appendix 1.

At the 47th meeting the MCC recommended that:

- trimethoprim should be reclassified from prescription medicine to 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
- Medsafe should review and be satisfied with the training material for pharmacists.

The extract of the minutes is attached in Appendix 2.

On 12 July 2012, trimethoprim was reclassified as a 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*.

After the 47th meeting, in a letter dated 9 July 2012, the New Zealand Medical Association raised concerns about prescriptions of trimethoprim being issued by pharmacists on first presentation. The response to this letter is attached in Appendix 3. The response states that in order to monitor the change of classification of trimethoprim in a robust manner, monitoring the use of a range of antibiotics across all prescribers as well as the rates of resistance of bacteria associated with urinary tract infection would be required. The response also stated that this data is routinely collected by other agencies (PHARMAC and ESR), and Medsafe will seek this information on an annual basis for several years to consider if a review of the reclassification is required.

Trimethoprim is classified as a prescription medicine in Australia.

3. Data from PHARMAC

PHARMAC is a New Zealand Crown Entity that decides, on behalf of District Health Boards, which medicines and pharmaceutical products are subsidised for use in the community and public hospitals.

PHARMAC provided the number of subsidised prescriptions (rounded to the nearest 10) for a range of medicines for the years (2007-2015) ending 31 December. The full data set is attached in Appendix 4.

Figure 1 shows the number of subsidised prescriptions for trimethoprim has increased from 2007 to 2015, however the percentage increase each year has reduced since the reclassification of trimethoprim in 2012. The amount of trimethoprim supplied by pharmacists under the reclassification is not included because the data is not available. Nitrofurantoin is included in Figure 1 for comparison.

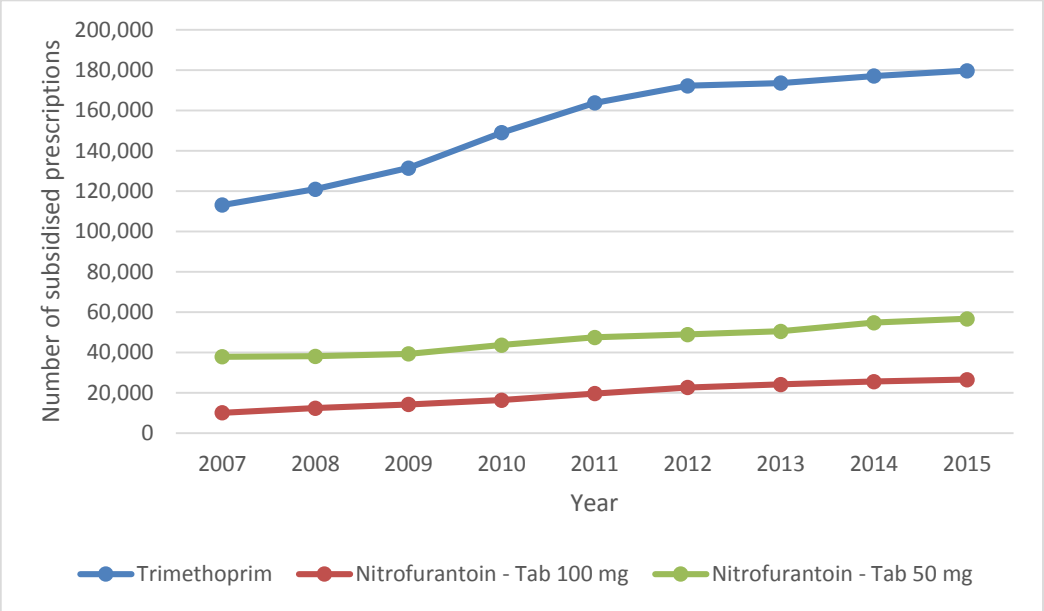

Figure 1: The number of subsidised prescriptions for trimethoprim and nitrofurantoin from 2007 - 2015

There has been a steady increase in the number of community dispensed prescriptions for trimethoprim since 2012. This small increase may reflect the increase in population rather than any change in prescribing habits. There has also been a steady increase in the use of nitrofurantoin. The earlier more dramatic increase appears to coincide with a reduction in use of norfloxacin.

4. Data from ESR

ESR (the Institute of Environmental Science and Research) is New Zealand's Crown Research Institute that specialises in science relating to people and communities.

ESR collects and collates national data on trimethoprim resistance among *Escherichia coli* isolated from urinary samples. ESR does not collect trimethoprim resistance data for any other urinary pathogen.

ESR collects the urinary *Escherichia coli* data on an annual basis from diagnostic laboratories throughout New Zealand. The data is available on their website. The graph in Figure 2 below (extracted from the data in Appendix 5) shows the national rate of trimethoprim and nitrofurantoin resistance among urinary *Escherichia coli* from 2007 to 2015. Nitrofurantoin is included in Figure 2 for comparison.

Figure 2 shows that the national rate of trimethoprim resistance among urinary *Escherichia coli* has increased and in 2015 was 26.1%.

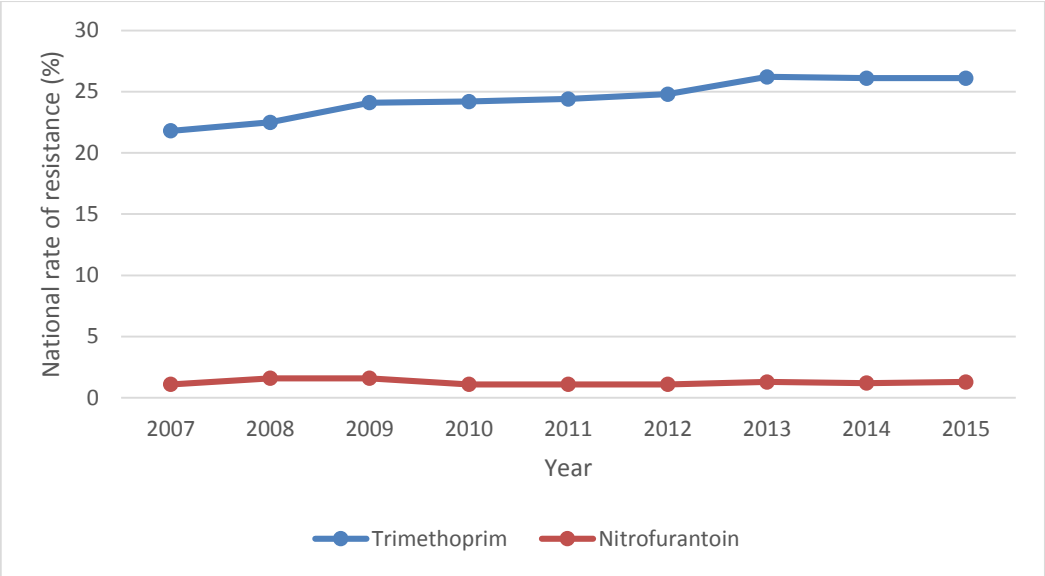

Figure 2: National rate of trimethoprim and nitrofurantoin resistance (in %) from 2007-2015

Trimethoprim resistance has been increasing, but there was no dramatic increase associated with the wider availability of trimethoprim. It should be noted that the first two years of analysis involved far fewer samples than the later time points and may not be as accurate as the later points.

The Department of Health in Australia publish antimicrobial resistance rates. In 2010 the national rate of resistance for trimethoprim was 21.2%[1] (in New Zealand it was 24.2%). In 2014 the national rate of resistance for trimethoprim was 29.2%[2] (in New Zealand it was 26.1%). The rate of resistance for trimethoprim has increased more in Australia where it is classified as a prescription medicine.

The BPAC (Best Practice Advocacy Centre New Zealand) guidelines (2017) for management of an uncomplicated urinary tract infection[3] state that urine culture is not necessary to diagnose cystitis. Urine culture is most useful for infections that are considered to be complicated due to an abnormality of the urinary tract, or other factors such as male, pregnancy, diabetes or renal failure, catheter, residential care facility, persistent or recurrent cystitis or atypical symptoms. For simple, uncomplicated urinary tract infections in women aged 16-69 years, the patient can be treated empirically with either trimethoprim 300 mg daily for three

days or nitrofurantoin 50 mg four times daily for five days. As sensitivity testing is not routinely performed for all women presenting with symptoms of a urinary tract infection, the sensitivity patterns reported by ESR are likely to represent only the subset of patients with 'complicated' urinary tract infections. It is therefore not clear whether the reported resistance to trimethoprim represents all cases of urinary tract infection or just those for whom a complicating feature was present (and therefore at greater risk of resistance).

With the information presented it is difficult to assess whether trimethoprim supplied by pharmacists under the reclassification has had an impact on the incidence of resistance to trimethoprim. It would be interesting to see how many patients who present to pharmacies for treatment have urinary tract infections that are resistant to trimethoprim (ie, what proportion of patients who receive a pharmacist prescription for a urinary tract infection end up getting a subsequent GP prescription for a second antimicrobial (with or without a urine culture and sensitivity). However, this would require funded research.

5. Conclusion

This information paper presents the data collected by Medsafe from PHARMAC and ESR. Given this information and the published resistance rates in Australia, Medsafe does not consider that a review of the reclassification is required at the current time.

Medsafe does consider that it would be useful, if resources allowed, to conduct impact analyses of reclassification decisions for other medicines.

6. References

1. Turnidge JD, Gottlieb T, Mitchell DH, et al. 2013. Australian Group on Antimicrobial Resistance Community-onset Gram-negative Surveillance Program annual report, 2010. *Communicable Diseases Intelligence* 37(3) 219-223.
   URL: http://www.health.gov.au/internet/main/publishing.nsf/content/cda-cdi3703-pdf-cnt.htm/$FILE/cdi3703d.pdf (accessed 18 January 2018).
2. Bell JM, Turnidge JD, Coombs GW, et al. 2016. Australian Group on Antimicrobial Resistance Australian Enterobacteriaceae Sepsis Outcome Programme annual report, 2014. *Communicable Diseases Intelligence* 40(2) 229-235.
   URL: http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-cdi4002-pdf-cnt.htm/$FILE/cdi4002g.pdf (accessed 18 January 2018).
3. Best Practice Advocacy Centre New Zealand. 2017. *Antibiotics: Choices for common infections*. URL: https://bpac.org.nz/antibiotics/bpacnz-antibiotics-guide.pdf (accessed 18 January 2018).