Submission for Reclassification of Trimethoprim

Part A

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

Trimethoprim

2. Proprietary name(s)

TMP®

Triprim® (now discontinued)

3. Name of company/organisation/individual requesting reclassification

Pharmacybrands Ltd, the parent company for Life, Unichem, Amcal, Radius and Care Pharmacies in New Zealand.

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

300mg tablets

5. Pack size and other qualifications

The change is sought for three tablets when supplied by a trained pharmacist to a woman aged 16 to 70 years with an uncomplicated urinary tract infection (see wording below).

6. Indications for which change is sought

For the treatment of acute uncomplicated lower urinary tract infections (UTI) in women aged 16 – 70 years with previous history of urinary tract infections

Empiric treatment for uncomplicated UTIs is recommended in women with trimethoprim or nitrofurantoin as first-line agents.[1,2] Thus, our recommendation is to supply what patients should generally be receiving anyway. Children and men will not be supplied without a prescription as medical consultation is important. Please see algorithm (Appendix 1) and training material proposal (Appendix 2).

7. Present classification of medicine

Prescription only medicine

8. Classification sought

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 NZ College of Pharmacists' training in the treatment of urinary tract infections.

OR Pharmacist-only Medicine when supplied in packs of three tablets to women aged 16-70 years for uncomplicated urinary tract infection, by a pharmacist who has successfully completed the NZ College of Pharmacists' training in the treatment of urinary tract infections.

Trimethoprim would be supplied as 300mg once a day for three days, as per BPAC guidelines.[1,2] Three days of antimicrobials is the recommended treatment for uncomplicated UTIs in other countries also.[3,4] The International Clinical Practice Guidelines recommends 3 days of co-trimoxazole (noting trimethoprim considered equivalent in some countries) as one of four alternatives for uncomplicated UTIs, depending on local resistance rates.[5]

We have considered the option of accreditation through the Pharmacy Council in a similar manner to the Emergency Contraceptive Pill. This is something the Pharmacy Council is unable to provide.

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

Trimethoprim is a prescription-only medicine in other developed countries.

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.[6] PGDs are available in many regions of the UK allowing pharmacists to supply trimethoprim without prescription. For trimethoprim the PGDs have included:

- Treatment of women only
- An age requirement: minimum age is usually 16 or 18, maximum age is usually 65 or 70
- Symptoms consistent with uncomplicated UTI
- Exclusion criteria include: symptoms of pyelonephritis or vaginal discharge, pregnancy, breastfeeding, renal disease, diabetes, catheterisation, allergy to trimethoprim, taking specified interacting medicines, recent treatment of a UTI (last four weeks)

Please see example PGDs (Appendix 3).

In the UK trimethoprim and nitrofurantoin have recently been considered for reclassification to pharmacy-only medicine including a public consultation

(trimethoprim public consultation attached as Appendix 4). Both applications have been withdrawn in 2010, and while there is no information about why they were withdrawn, it has been speculated that this was because of concerns about development of resistance.[7] The UK does not have a pharmacist-only category for supply of non-prescription medicines, nor do they have any medicines scheduled as non-prescription only when supplied by an accredited or specifically trained pharmacist. Thus, the non-prescription supply that was proposed in the UK is different in a number of key areas to our proposal.

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

For 12 months to September 2011 30,100 packs of trimethoprim 300mg tablets (50 per pack) were supplied in the NZ market according to IMS. As a number of other countries also have trimethoprim as first-line treatment for UTIs, usage is expected to be substantial around the world. As the UK uses different dosing to NZ, 200mg twice daily, their data would reflect the 200mg tablet. Trimethoprim has had substantial use internationally combined with sulphamethoxazole in co-trimoxazole.

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

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

No new labelling is proposed for the new presentation. The current labelling will not be used for non-prescription supply as the pack size is too large. The medicine will be dispensed by a pharmacist into a bottle of three tablets and labelled with the patient's name.

It is proposed to mandate that an information leaflet for the non-prescription medicine (see Appendix 5) is supplied with the medicine. This will be provided to pharmacists when they have successfully completed the training course, and will be available for downloading from the Pharmacybrands, Pharmaceutical Society and Pharmacy Guild sites. Having the information sheet available for downloading for everyone may have a slight risk of usage without training, so a warning will be added that it is only to be supplied by pharmacists who have successfully completed the appropriate training. Additionally pharmacists will be encouraged to display training certificates in store.

12. Proposed warning statements if applicable

Should a manufacturer decide to supply a pack of three tablets, proposed warning statements should be considered. Assuming that such a pack is not provided, an information leaflet must be provided when supplying non-prescription trimethoprim to consumers, see Appendix 5.

13. Other products containing the same active ingredient(s) and which would be affected by the proposed change.

TMP tablets are the only brand of trimethoprim currently on the NZ market. Combination products (co-trimoxazole) would be unaffected by this change.

Part B

1. A statement of the benefits to both the consumer and to the public expected from the proposed change

There are multiple beneficiaries of this proposal as outlined below.

One of the most common acute reasons for medical consultation in young women is acute uncomplicated lower urinary tract infection.[8] Urinary tract infections (UTIs) are the second most common reason for empirical antimicrobial treatment, are not considered a serious disease[8] and are self-diagnosable by women who have previously experienced the condition.[3] Urinary tract infections (UTIs) occur in over 30-50%[3,8] of women in their lifetime.

The primary beneficiary of this reclassification is expected to be the consumer, most importantly because of convenience of access to treat a condition that can start at any time, causes discomfort and distress, and may result in time away from work or non-work activities. The consumer will also benefit from saving in costs – cost of the doctor's visit (which may include travel costs), and cost of time off work to get to the doctor. After hours and weekend appointments may cost $70. Pharmacists are qualified health professionals who are already consulting in this area, but will be upskilled to provide responsible supplies of antibacterials. Extended hours pharmacies are available in many areas and no appointment is required. Based on the high uptake of the Emergency Contraceptive Pill accreditation, we anticipate strong uptake of UTI training.

Other possible beneficiaries are as follows:

- Health funding in NZ will benefit, providing public benefit through health dollars better spent. BPAC considers urine cultures are unnecessarily being performed in uncomplicated UTIs, noting that over $12.5 million was spent on nearly 800,000 urine cultures in 2005.[1] The cost to the NZ health system of the medicine and dispensing fee is a further saving should people choose to pay themselves instead
- GPs should benefit, particularly in rural areas or other areas in which GP services are under pressure. Population growth, an aging population and developments in health are increasing demand for health services in a constrained fiscal environment. These require better use of the existing health workforce, including extending existing roles.[9]
- Doctors may be more accessible or able to do more on complex chronic care cases if seeing less minor ailments.
- Pharmacists will appreciate being better able to use their clinical skills from their four year degree course, and will appreciate being able to provide more assistance to consumers requesting advice. A majority of community pharmacists will train to supply this product. As the topics covered include bacterial resistance, STIs and privacy, the training has potential benefits in areas other than UTIs also.

- Having a first-line UTI treatment (trimethoprim) available in a short course more readily than second-line is a logical mechanism to reduce inappropriate usage of second-line treatment, and unnecessary longer use that can increase resistance,[10] which may have public health benefits.
- Employers can benefit through prompt treatment of employees, reduced time off for symptoms and doctor visit. Productivity gains provide public benefit.
- Patients may currently use left-over antibiotics (from previous doctor supply, potentially for any condition) when they cannot get to the doctor. Being able to get to the pharmacy for immediate appropriate treatment lessens the need for using left-overs, provides a triage service and ensures treatment is more appropriate than a best-guess from home.
- Doctors will not need to supply extra antibiotics to cover further episodes (which is against the good antimicrobial practice recommendations of shortest course possible to ensure no left-overs).[11,12]

According to BPAC (April 2011), first-line treatment of uncomplicated lower urinary tract infections is either trimethoprim 300mg once daily for three days or nitrofurantoin 50mg four times a day for five days.[2] As emphasised by BPAC in 2011, because of resistance concerns and broad-spectrum of action, norfloxacin should only be used second-line in recurrent UTI or second-line in acute UTI, where trimethoprim or nitrofurantoin have failed.[13] Scottish Intercollegiate Guidelines Network (SIGN) guidelines also recommend three days' treatment with trimethoprim as a first-line option.[4]

We have chosen trimethoprim as the preferred pharmacist-supply medicine, rather than nitrofurantoin primarily because, at 300mg once daily for three days, compliance is likely to be better than with nitrofurantoin four times a day for 5 – 7 days and there is unlikely to be any medicine left over for another time.

The vast majority of uncomplicated UTIs are caused by *Escherichia coli* (80-90%), the remainder are caused by *Staphylococcus saprophyticus* (5-10%) and the rest by *Proteus*, *Pseudomonas*, *Klebsiella* and *Enterobacter* species.[3,8] Trimethoprim, a diaminopyrimidine antibacterial agent, inhibits dihydrofolate reductase with a much greater affinity for this enzyme in bacteria than in mammals.[10] Although often combined with sulphamethoxazole as co-trimoxazole, "...trimethoprim alone is probably as effective and less toxic," so is preferred.[10] Being excreted primarily by the kidneys, trimethoprim achieves high concentrations in the urine.[10] Trimethoprim is ineffective against *Pseudomonas*, but has good effectiveness against *Staph saprophyticus*, *Klebsiella*, *Proteus* and *Enterobacter* according to the susceptibility report for Auckland (Appendix 6). Effectiveness against *E.coli* is good taking into account the likelihood of higher rates of resistance bacteria in samples tested compared with community.[14]

2. Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated

Cystitis is defined as a lower UTI with symptoms of dysuria and frequent and urgent urination.[3] Fever is uncommon (and would require referral). Four in five people who report having cystitis or UTIs are women.[3] Diagnosis is usually straightforward – women with classical presentation of uncomplicated UTI without vaginal discharge or

irritation have a 90% probability of UTI.[1] UTIs are not a serious disease[8] and are self-diagnosable by women who have previously experienced the condition.[3]

Empiric treatment is recommended for uncomplicated lower UTIs; urine culture is not recommended and does not improve outcomes.[1] Dipstick urinalysis is not necessary unless the diagnosis is in doubt;[1] where there is doubt, pharmacists are to refer for GP consultation. Thus, dipsticks are not included in the algorithm. Scottish Intercollegiate Guidelines Network (SIGN) confirms that tests that suggest or prove the presence of bacteria or white cells in the urine rarely have important implications for diagnosis.[4]

Pharmacists have previously triaged UTIs, referring to the doctor, giving lifestyle advice, or providing a urinary alkaliniser. However, given the importance of minimising risk of bacterial resistance and ensuring best practice, we are advocating that only pharmacists who are trained specifically for this are able to supply trimethoprim, and an algorithm is provided to pharmacists; this is in line with supply by pharmacists in the UK under patient group directions (PGD).

Training of the pharmacist will be mandatory, with successful completion of a College of Pharmacists course required. This training will include:

- Relevant physiology
- Relevant microbiology
- Causes and symptoms of UTIs
- Differential diagnosis including STIs, uncomplicated vs complicated UTI, acute pyelonephritis (based on discussion of symptoms/history in a pharmacy consultation)
- Sexually transmitted infections – incidence, symptoms, risk factors, how to discuss, when to refer for checks
- Questioning techniques
- Warning signs/referral points
- Treatment options for UTIs including non-treatment
- Antibacterial resistance and appropriate supply of antibacterials
- Trimethoprim – CI, precautions, adverse effects, interactions, duration of use, resistance
- Use of protocol/consultation pad to guide the pharmacist through an appropriate assessment
- Preventative strategies including cranberry

Additional requirements for supply are:

- Pharmacy has to have a private consultation area
- Product can only be supplied in a pack of three tablets
- Product cannot be supplied in advance of need
- Product must be supplied with information sheet
- Consultation including patient history is documented
- GP is advised by the pharmacist if the patient agrees (proforma letter supplied)

Pyelonephritis symptoms will be referred, i.e.:

- Fever and chills
- Flank pain
- Varying degrees of dysuria, urgency, frequency
- Nausea and vomiting

Complicated UTIs will be referred, i.e. patients:[1,3]

- With recurrent UTIs (more than three UTIs in a year)
- with abnormal urinary tract, e.g. stone, reflux, catheter
- with prior urologic surgery
- with a history of renal stones
- with renal impairment
- with spinal cord injury
- with recent urinary tract instrumentation
- with likely hospital-acquired infections
- who are pregnant
- who are immunocompromised
- who are male
- who are children

Other referrals will include:

- Women with no previous history of UTI
- Women using any antibiotic in the last six months
- Women over 70 years
- Inadequate response after three days, or relapse
- Women with hypersensitivity to trimethoprim, blood dyscrasias, porphyria or impaired renal function
- Women with previous failure to trimethoprim
- Symptoms that suggest upper UTI infection, e.g. flank pain, fever and chills
- At risk of sexually transmitted infections (STIs) – this will be defined in the training material and algorithm
- Women with diabetes mellitus where control is suspected to be inadequate

Sexually transmitted infections

Sexually transmitted infections may be mistaken as UTIs. Pharmacists are already aware of STIs when supplying vaginal antifungals and in advising on the emergency contraceptive pill. In a patient with symptoms of UTI and at risk sexual history, *Chlamydia trachomatis* should be considered,[1] which should prompt referral. Training will include STIs, risk factors and symptoms.

3. Relevant comparative data for like compounds

Currently antibacterials for urinary tract infections are prescription-only in NZ except methenamine hippurate, which is not considered appropriate for treatment of urinary tract infections.[15] Other antimicrobials available without prescription in NZ include:

- Topical azoles for vaginal candidiasis (pharmacist-only medicine)
- Single-dose oral fluconazole for vaginal candidiasis (pharmacist-only medicine)
- Topical antivirals for herpes labialis (general sales)
- Single dose oral antiviral (famciclovir) for herpes labialis (pharmacist-only medicine)
- Oral oseltamivir for treatment of influenza (exemption to prescription with pharmacist supply under strict criteria)
- Topical antifungals for external use for conditions such as tinea pedis and pityriasis versicolour (pharmacy only and general sales)
- Povidone iodine for skin infections and throat infections

Other OTC products available in NZ

Symptomatic relief for UTIs is possible with urinary alkalinisers which are available for sale in the pharmacy.

Methenamine hippurate is available as a general sales medicine, but has no real place in management of acute UTIs.[15]

Cranberry products are available in pharmacy. Cranberry may be useful preventing UTIs in susceptible women, but does not have a place in management of acute UTIs.[1]

4. Local data or special considerations relating to New Zealand

Local data of antimicrobial susceptibility suggests a 73% susceptibility of trimethoprim to *Escherichia coli* from Labtests Auckland 2010 (Appendix 6). Many of these cultures will be in complicated UTIs rather than empirically treated UTIs, and current BPAC guidelines for NZ continue to have trimethoprim and nitrofurantoin first line treatments for uncomplicated UTIs.[2]

Should guidelines change in the future, this reclassification could be reviewed and a different first-line agent be chosen instead for availability through the pharmacist. Trimethoprim has been chosen for this application due to the ease of taking 300mg once daily for three days which is likely to maximise compliance.

Chlamydia trachomatis, is a common condition in sexually active people in NZ, occurring in around 5% of pregnant women, 2% of sexually active secondary school students and 3% of women attending a university health clinic.[16] Being usually asymptomatic, it should be considered in people with a UTI who are at risk of STIs. The algorithm and training will include screening for risk factors (e.g. irregular use of condoms, previous STI)[16] and referral for STI check as appropriate. Chlamydia screening and treatment through pharmacy occurs in the UK, and this would be a

good follow-on from UTI treatment in NZ increasing accessibility to this test here as well. Training for pharmacists will also include other STIs.

5. Interactions with other medicines

From the NZ-approved datasheet the following interactions are possible:[17]

- Pyrimethamine as malarial prophylaxis (discontinued in NZ)
- Potentiated anticoagulant activity of warfarin (Stockley's notes this is likely to be minor)[18]
- Prolongs half-life of phenytoin
- Cyclosporin – reversible deterioration in renal function
- Increased levels of procainamide, amantadine
- Increased plasma digoxin levels in elderly
- Additive effect with other anti-folate medicines e.g. methotrexate (potential for bone marrow depression)[18]

Stockley's reports also:[18]

- Additive hyperkalaemic effects possible with other agents causing hyperkalaemia
- Hyponatraemia with thiazide diuretics
- Increased dapsone toxicity
- Increased plasma levels of lamivudine, zalcitabine and zidovudine
- Increased plasma levels of repaglinide

Given the three day course used, many of these interactions are unlikely to be important, however, warfarin, phenytoin, digoxin (in elderly) and methotrexate appear most important for this time period based on Stockley's Drug Interactions text. Some of these medicines interact with other OTC medicines e.g. anti-inflammatories and omeprazole. Pharmacists receive training in drug interactions and are required to advise on interactions in normal practice. However, this will be reiterated in the training provided by the College of Pharmacists.

No interaction between trimethoprim and the oral contraceptive is apparent in the datasheet[17] or Stockley's.[18] The UK consultation document likewise considers contraceptive control to be unlikely to be affected by three days' treatment with trimethoprim.

6. Contraindications

Pregnancy: On theoretical grounds (effect on folate), trimethoprim should be avoided in the first trimester of pregnancy.[19]

The following is extracted from the datasheet:[17]

> *"The safety of trimethoprim in human pregnancy has not been established. At doses greatly in excess of the recommended human therapeutic dose trimethoprim has been reported to be teratogenic in rats with effects typical of a*

folate antagonist and preventable by administration of dietary folate. No significant medicine-related malformations have been demonstrated in rabbits but at doses approximately ten times in excess of the human therapeutic dose an increase in fetal deaths was noted."

Women who are pregnant or who think they could be pregnant will be referred to the GP, as this is not an uncomplicated UTI. The algorithm, training and consumer leaflet will emphasise the need to check pregnancy status and refer. However, it is possible that a woman unknowingly in the early stages of an unplanned pregnancy might be treated with trimethoprim (as might also occur through a doctor's visit).

Briggs' Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk (8th Ed, 2008),[20] reports that trimethoprim crosses the placenta, with similar levels in foetal and maternal serum and amniotic fluid. Some studies (including placebo-controlled trials involving several hundred patients) did not demonstrate an increase in foetal abnormalities, but other data indicates that structural defects occur more often when trimethoprim is given in the first trimester, and that folic acid supplementation may reduce this risk. Thus, trimethoprim should be avoided in the first trimester of pregnancy. The preferred treatment in pregnancy is nitrofurantoin (except in the last few weeks of pregnancy).[19] In the rare case that a woman who is unknowingly pregnant takes trimethoprim OTC, the course is short (only three days) which limits the effect on folate. The data above is likely to be generated from longer courses.

Low concentrations of trimethoprim are found in breast-milk, representing a "negligible risk" to the infant, and the American Academy of Paediatrics considers trimethoprim use compatible with breastfeeding.[20]

7. Possible resistance

Resistance is an important consideration in treating UTIs. For example, norfloxacin should only be used in case of first line treatment failure,[13] and a three day course should be used for uncomplicated UTI to reduce risk of resistance and adverse events.[10] Current guidelines in NZ (BPAC), in the UK (Scottish Intercollegiate Guidelines Network) and internationally, recommend trimethoprim or nitrofurantoin first line for uncomplicated UTIs.[2,4,5]

"The challenge in treating UTIs is to only treat those who need it, with the correct antibiotic, for as short a time as possible. This benefits the patient and limits the development of bacterial resistance as much as possible."

Dr Michael Pontari, Journal of Urology, December 2011[11]

Furthermore, Dryden et al included in their list of "Actions to optimize antibiotic prescribing":[12]

- Prescribe in accordance with local and national policies and guidelines, avoiding broad-spectrum agents
- Prescribe the shortest antibiotic course likely to be effective. Using more than three days of antibiotic treatment in an uncomplicated UTI "...does not

increase the chance of success, but does increase the risk of selection of resistance bacteria in the gut flora and adverse drug effects."[10]

- Select agents with a view to minimising collateral damage

These recommendations provide the rationale behind the proposed reclassification of trimethoprim 300mg once daily for three nights under a mandatory training scheme which will emphasise antibacterial sparing strategies. Such strategies include the option of delaying antibiotic use in UTIs with minor symptoms, the importance of avoiding antibiotics if uncertain in the diagnosis (referral or wait and see approach as appropriate instead), and general advice about appropriate use of antibiotics.

Local data of antimicrobial susceptibility suggests a 73% susceptibility of trimethoprim to *Escherichia coli* from Labtests Auckland 2010 (Appendix 6). Many of these cultures will be in complicated UTIs rather than empirically treated UTIs. Research using urine cultures in uncomplicated UTIs show resistance is lower in practice than suggested by reporting of usual selected cultures, a study in the UK showed 24-27% resistance at the local laboratory for routinely submitted urines for culture, versus 14% in uncomplicated UTI patients.[14] Furthermore, only 4% of those uncomplicated UTI patients treated with three days of trimethoprim reconsulted with unresolved symptoms and a resistant isolate. Current BPAC guidelines for NZ continue to have trimethoprim and nitrofurantoin first line treatments for uncomplicated UTIs.[2]

Repeated or prolonged treatment of recurrent UTIs is likely to contribute to resistance.[4] Trimethoprim should be avoided if used in a UTI in the previous three months.[5] However, the pharmacist training and the algorithm will recommend referral with any oral antibiotic usage in the past 6 months, in line with research[21] and the UK consultation document.[22] Additionally, resistance to trimethoprim is higher in women with more than three UTIs per year (who will be referred under our algorithm).[14] The SIGN guidelines note: "women with recurrent UTI should be advised to take cranberry products to reduce the frequency of recurrence", despite the optimal dose not being known.[4] There appears to be less evidence for methenamine hippurate but SIGN guidelines note: "methamine hippurate may be used to prevent symptomatic UTI in patients without known upper renal tract abnormalities."

A further requirement of supply will be to tell the healthcare consumer's GP of the supply of trimethoprim (with the consumer's permission). This ensures the GP does not reuse trimethoprim in case of treatment failure, and helps ensure complete records are held.

Confidence in ability of pharmacists to manage this well also comes from other pharmacist supplies. For the previously reclassified oseltamivir, available through pharmacists under strict criteria, research indicates that NZ community pharmacists have taken the opportunity to supply oseltamivir seriously, updating themselves and generally supplying the medicine responsibly and conservatively.[23] Consultation materials were well-regarded and kept for use in case of oseltamivir consultation. For fluconazole and aciclovir in the UK there is no evidence of increased resistance from 10 years of OTC availability.[10] The text Antimicrobial Chemotherapy considers that extension of antibiotic supply to other healthcare professionals requires appropriate

training and education and the availability of carefully constructed guidelines.[10] Pharmacists and nurses may be better at following protocols for supply of medicines than doctors.[24]

In summary, we believe the supply of trimethoprim 300mg per day for three days for uncomplicated UTIs by a trained pharmacist following an algorithm provides a number of benefits while minimising potential for overuse. This scheme is similar to that provided in the UK PGDs for trimethoprim. We could not find criticism of these in the literature, and PGDs for trimethoprim are still in use in parts of the UK. We consider that this very controlled environment, including consumer information that highlights the option of not taking antibiotics, provides a responsible approach to minimising resistance. We expect antibacterial treatment of UTIs will not substantially increase in this environment, but rather that it better uses the pharmacist in improving timely access to primary care for patients with discomfort and an acute need for a treatment.

8. Adverse events - nature, frequency etc.

Adverse events with trimethoprim include rash, pruritis, photosensitivity, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrosis and aseptic meningitis. The UK consultation document from the MHRA on reclassification of trimethoprim reported:[22]

> *"The common side effects are minor and do not preclude OTC use."*
>
> *"It is not possible to predict which individuals will experience these rare but serious side effects. However they are no more likely to experience them having been supplied the product by a pharmacist compared to having [been] prescribed it by a doctor."*

9. Potential for abuse or misuse.

There is no potential for abuse.

Potential for misuse is low given the uncomplicated dose, three tablet provision, the supply by trained, trained pharmacists, and the reminder to finish the course that is standard practice on dispensing labels for antibiotics, and the reminder in the consumer leaflet to finish the course.

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