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Submission for the Reclassification of Nitrofurantoin

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Application to Reclassify Nitrofurantoin from Prescription Medicine to Allow Pharmacist-only Supply

Executive Summary

In 2012, trimethoprim became available in New Zealand without a prescription through the reclassification process. This process allowed specifically trained pharmacists, to dispense trimethoprim to women between the age of 16-65 years who had suspected uncomplicated cystitis and who fit specific criteria.[1] These criteria were used to identify a small subset of people with suspected urinary tract infections to whom supply was reasonable. This supply was consistent with New Zealand guidelines.[2]

In women with cystitis, the frequency of bacterial resistance to trimethoprim increases if they have had treatment with trimethoprim or another antibiotic in the last six months.[3] Therefore we took the cautious approach of referring such patients who confirmed this to the doctor rather than treating them in the pharmacy. However, New Zealand,[4] Scottish[5] and American[6] guidelines do not differentiate such women as being managed differently from other patients. Many women presenting in pharmacy have taken antibiotics in the last six months and therefore are not eligible for treatment under the existing trimethoprim reclassification and have no option of pharmacist supply.

This reclassification application will allow an appropriate first-line agent for uncomplicated cystitis, nitrofurantoin, to be supplied by pharmacists without a prescription in cases where women have had a systemic antibiotic in the last six months, or where a contraindication or precaution exists for trimethoprim but not for nitrofurantoin. In other cases where a woman with cystitis can be treated by the pharmacist, and no contraindications exist, the pharmacist and patient can collaboratively decide on either trimethoprim or nitrofurantoin for the treatment.

Escherichia coli (the primary cause of cystitis in the community) has very high susceptibility with nitrofurantoin internationally,[7-9] and in New Zealand ,[10] with low bacterial resistance, including in countries like the Netherlands where usage is relatively high.[7]

The benefit of reclassifying nitrofurantoin is that women, who can be in considerable discomfort, are not unnecessarily delayed from appropriate treatment because they have received antibiotics in the last six months. Efficacy may increase given the higher rate of susceptibility in *E. coli* with nitrofurantoin than trimethoprim in New Zealand.[10] Further benefits include reduced use of trimethoprim, norfloxacin and other antibiotics (broad spectrum) that are likely to be prescribed by the doctor in many of the cases in which antibiotics have been prescribed in the past six months. The supply will be best practice according to New Zealand guidelines, which is designed to potentially minimise resistance and adverse effects and maximise patient benefit.

For short term use, nitrofurantoin is considered to be well-tolerated. It is likely that the reputation nitrofurantoin has for gastrointestinal reactions harks back to earlier times when higher doses and longer durations were used. This is very much a dose-related effect and also occurs with slow release formulations and intravenous administration.[11]

For patient safety, the most concerning adverse reaction with nitrofurantoin has been its chronic lung toxicity which has been highlighted in three Prescriber Update articles.[12-14] Nitrofurantoin has a risk of

acute pulmonary toxicity (a hypersensitivity reaction), and therefore, pharmacists will check for previous history of reactions (including respiratory illness type symptoms) with nitrofurantoin and will warn women of this rare effect (and explain action to take if it occurs). Furthermore, this reaction typically resolves in one to three days of discontinuing therapy.[15] Notably, nitrofurantoin remains first-line in many countries for uncomplicated cystitis despite this reaction, and in the Netherlands, approximately 66% of uncomplicated cystitis in women is treated with this agent.[7] Other hypersensitivity reactions can occur, as with other medicines that are available without prescription. The importance of informing CARM and the patient's regular doctor of any side effect with nitrofurantoin will be emphasised in pharmacists' training. Additionally, the importance of informing the patient's doctor of a nitrofurantoin supply (unless the patient requests otherwise) will be emphasised. A new screening tool, algorithm for supply, and information sheet are currently completing consultation.

The proposed reclassification would require that the pharmacist has undergone the training that was required to be able to supply trimethoprim (see the appendices). It is proposed not to make further training mandatory, as pharmacists have a professional obligation as outlined in ethical conduct requirement clauses of the New Zealand Pharmacy Council to remain up-to-date. However, training around nitrofurantoin specific to the reclassification will be available to pharmacists, and it is expected that most pharmacists will do this. The datasheet is also readily available. The screening tool and algorithm will clearly indicate when nitrofurantoin can and cannot be supplied. The tools would be circulated through Green Cross Health to all its members, and also through other pharmacy organisations such as the Pharmaceutical Society and Pharmacy Guild of New Zealand.

Pharmacists in New Zealand have really stepped up in the last few years. Pharmacists are providing patient centric services such as warfarin monitoring, vaccinations, Long Term Condition patient management (as per the Community Pharmacy Services Agreement), and a number of medication adherence services. Pharmacy as an industry has become proactive, driving new initiatives, working with the Ministry of Health on medicines policy, and setting up a joint vision between the New Zealand Medical Association and New Zealand Pharmaceutical Society. Pharmacists have also worked to collect research on the new initiatives, with published research on the warfarin initiative showing positive outcomes,[16] research in vaccination showing pharmacy reached people with influenza vaccination who had not accessed it the previous year (usually because they had been too busy),[17] and with 82% of randomly selected pharmacies taking part in research to help ascertain outcomes from the Trimethoprim reclassification.[18] This reclassification is a further extension of the very careful approach being taken by pharmacists to maximise public safety and potential benefits of new initiatives. Research of New Zealand pharmacists show they want to facilitate greater contribution to patient care and want greater involvement in setting health policy.[19]

Pharmacists have been continuing to show their willingness to assist in achieving the Minister of Health's objectives of Better, Sooner, More Convenient healthcare (with the Honourable Tony Ryall). The incoming Minister of Health, the Honourable Jonathan Coleman has recommended that, in light of challenges to the New Zealand health sector, despite an increased budget from $11.8 billion in 2008/9 to $15.6 billion in 2014/15, New Zealand needs new and innovative ways of managing pressures to the health system.[20] Pharmacists are keen to assist in this endeavour, with the proposal in this application.

Pharmacists are committed to better health outcomes for New Zealanders, care closer to home, and supporting people to manage their own health in their own homes, in an integrated way, in line with the Honourable Jonathan Coleman's views.[20] Dr Coleman is keen to see the role of pharmacists being

maximised.[21] The Honourable Peter Dunne stated "we think there's much greater scope for pharmacists to play a much more significant role than they play already". This reclassification provides benefits for women with a very uncomfortable condition, and is working in an integrated fashion within New Zealand health policy.

Background

In 2012, the Medicines Classification Committee recommended that trimethoprim be reclassified to allow specifically trained pharmacists to supply it under strict criteria.[1] The resulting gazettal notice was for trimethoprim to be 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".[22]

The College of Pharmacists' training became available from November 2012. The course takes approximately four to five hours including pre-reading and builds on the underlying pharmacists' knowledge (see the appendices for further details). A 100% pass rate is required in the test for the pharmacist to have successfully completed the course. There is a screening tool to clearly identify those who fit the criteria for supply, and an algorithm for supply. A patient information sheet is given with each supply. Pharmacists are expected to inform the doctor of supplies unless the patient does not consent, which pharmacists tell us occurs very infrequently. The strict criteria included specific symptoms, and excluded certain ages, comorbidities, and males, as well as recent hospitalisation or antibiotic use (see screening tool for trimethoprim attached in the appendices). A very careful and considered approach was taken to minimise the risks of increasing antibiotic resistance, including non-supply in the case of antibiotic use (trimethoprim or other systemic agent) in the past six months, despite this not being discussed in the Best Practice Advisory Centre (BPAC) Guidelines.

Subsequently 1785 community pharmacists have successfully completed this training, and women who meet the criteria for supply can access this medicine at most New Zealand community pharmacies. [redacted]

1. **International Non-proprietary Name**
   Nitrofurantoin

2. **Proprietary name(s).**
   Nitrofurantoin is available in New Zealand as the following brand:
   Nifuran 50 mg and 100 mg tablets, from WM Bamford and Co Ltd

   Macrodantin capsules (25 mg, 50 mg and 100 mg) from Pharmaco has had the product approval lapse, as has Furadantin oral suspension 25 mg/5 mL from Pharmacia.

3. **Name of the company / organisation / individual requesting a reclassification**
   Green Cross Health Ltd. (the parent company for Life and Unichem pharmacies in New Zealand and Pharma Projects Ltd. Neither are sponsors for the medicine.

4. **Dose form(s) and strength(s) for which a change is sought.**
   The change is sought for solid dosage forms. Current BPAC guidelines suggest that the appropriate strength for supply of nitrofurantoin is 50 mg.

5. **Pack size and other qualifications**
   We propose that nitrofurantoin 50 mg is supplied according to New Zealand's Best Practice Advisory Centre (BPAC) guidelines for uncomplicated urinary tract infection, which currently recommends 50 mg four times daily for five days.[4]

   We propose using similar qualifications as for trimethoprim. The trimethoprim availability is as follows: prescription only, 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.

   We propose that nitrofurantoin can be supplied by pharmacists who have successfully completed the College of Pharmacists' training course under the same conditions as for trimethoprim as well as where antibiotics have been used in the last 6 months (including for cystitis).

   We suggest the following wording, but Medsafe may have suitable alternatives:
   Prescription only except in medicines for oral use containing 50 milligrams per dose unit when sold in a pack of 20 solid dosage units to a woman aged 16-65 years for the treatment of an uncomplicated lower urinary tract infection by a registered pharmacist who has successfully completed the New Zealand College of Pharmacists' training course in the treatment of urinary tract infections, where supply adheres to the screening tools approved by the Pharmaceutical Society of New Zealand.

We have suggested outlining the need to adhere to the screening tools to clearly indicate to pharmacy that the medicine is prescription only if there is deviation from that form. However, this is not essential.

6. **Indications for which change is sought**
   Uncomplicated cystitis in women aged 16-65 years

7. **Present classification of the medicine**
   Prescription-only

8. **Classification sought**
   Pharmacist-only medicine, or exemption to prescription. There is no preference.

9. **Classification status in other countries (especially Australia, UK, USA, Canada).**
   Prescription-only medicine

10. **Extent of usage in New Zealand and elsewhere and dates of original consent to distribute.**
    Please see Appendix 1 for usage data.

    Nifuran tablets and Furadantin suspension were registered in New Zealand in 1969. Macrodantin was registered in 1977. Only Nifuran remains on the market currently.

11. **Labelling or draft labelling for the proposed new presentation(s).**
    The current pack size is 100 tablets. With the BPAC guidelines, 20 tablets would be dispensed from the bulk container. No change to manufacturer labelling is envisaged as the pharmacist would dispense and label for that patient. However, there would be a consumer information sheet provided (Appendix 2).

12. **Proposed warning statements if applicable.**
    See screening tool (Appendix 3), information sheet (Appendix 2) and algorithm (Appendix 4).

13. **Other products containing the same active ingredient(s) and which would be affected by the proposed change.**
    None

Reasons for requesting reclassification change including benefit-risk analysis.

Multiple benefits exist for this reclassification. To summarise: the primary benefit is to women who otherwise may have to wait for treatment. Other benefits include: increased adherence to best practice guidelines for treatment of uncomplicated cystitis; benefits for taxpayer funded health and the health system in general; further knowledge for pharmacists in an area already managed by them; relief for busy doctors; and benefits for employers and the New Zealand economy in reduced absenteeism. These are all expanded upon below.

> *"Our health system is going to continue to face pressures and we are going to need to produce new and innovative ways of addressing those pressures."* The Honourable Jonathan Coleman, Nov 2014[20]

> *"It is important that we continue to look for innovative new approaches that support the desire of people to take responsibility and play a more active role in their own healthcare.... These flexible, innovative approaches are showing up across the health service. Pharmacists, doctors, nurses and patients are increasingly working together in new and different ways. Future switches from prescription to over the counter availability will inevitably involve more potent medicines and we have seen a tangible example of this trend in the recent switch involving the antibiotic trimethoprim."* The Honourable Tony Ryall, October 2012[23]

Health Ministers have been clear, New Zealand needs innovation in our delivery of health services to help reduce pressure on health resources and provide patient-centric services. This application follows on from the innovative trimethoprim reclassification to widen the subset of women with symptoms suggesting uncomplicated cystitis who can be treated by a pharmacist.

The trimethoprim reclassification excludes supply to women who had taken antibiotics in the last six months (owing to the increased risk of bacterial resistance to trimethoprim following antibiotic use[3]). In this application we propose widening the criteria to allow women who have had antibiotics in this time (but who fit other criteria) to receive nitrofurantoin through specifically trained pharmacists.

Benefits to the consumer, public and others expected from the proposed change

See the Brass et al model[24] in Appendix 5 for an overview of benefits and risk.

One of the most common acute reasons for medical consultation in young women is acute uncomplicated lower urinary tract infection (cystitis).[25] Such infections are the second most common reason for empirical antimicrobial treatment, and are not considered a serious disease.[25] Cystitis is self-diagnosable by women who have previously experienced the condition.[26]

The reclassification of trimethoprim has contributed towards the Ministry of Health's 'Better, Sooner, More Convenient' healthcare model, delivering effective treatment promptly to women, and within Health Workforce New Zealand's desire to see health professionals working to the top of their scopes of practice.[27] However, under the model of supply with trimethoprim, women who have had systemic antibiotics of any kind for any reason in the six months prior to presenting in the pharmacy are referred to the doctor for care and cannot be supplied trimethoprim by the pharmacist. This is a conservative approach to take with trimethoprim given BPAC guidelines do not provide different management instructions for women who have received antibiotics in the last six months.

Primary benefit: to help women with a very uncomfortable condition

The primary reason to request this reclassification is for the benefit of women with uncomplicated cystitis who have had an antibiotic in the last six months.

Supply of recommended first-line treatment through specially trained pharmacists means that most women in New Zealand who have uncomplicated cystitis will be able to access an effective treatment for cystitis up to seven days a week without an appointment and with little waiting time. For a woman with an infection during the weekend or on a public holiday, this additionally may mean a saving of after-hours charges and, more importantly, a delay in accessing care. Cystitis can have a sudden onset and is often very uncomfortable. Women may have difficulties in getting to their doctor for treatment, given that cystitis does not confine itself to an onset during the working week, and that most women in the target age range work and would need to take time off work to attend a doctor for an appointment.

New Zealand women have a choice of a number of providers with medicines such as the emergency contraceptive pill and vaginal thrush treatments. Sometimes the choice remains weighted owing to funding of the medicine, or a woman may choose to see a doctor owing to particular concerns she may have, on referral from the pharmacist, or for other reasons. However, it is clear that where there is a choice, many women will choose to go to the pharmacy rather than the doctor for a medicine they need at short notice. For example, in Sweden, 93% of women chose to use the pharmacy rather than the doctor for vaginal antifungals.[28] In the UK, about a third of women chose to source the emergency contraceptive pill from the pharmacy rather than using the traditional sources in the two years after the reclassification.[29] A survey conducted through NZ Girl[a] found that a quarter of women answering this survey, who had had a UTI, went to the pharmacy first for treatment – this would have been answered on their experience prior to trimethoprim being available. Only 18% of women answering this survey had not been to a pharmacist for treatment or advice in the past 12 months. Of those who had, 86% rated their experience excellent or good. Of those who had been to a pharmacist for treatment or advice in the past 12 months, the best part of this experience was the convenience (78%), no need for an appointment (77%), good advice or treatment (46%) and reduced waiting time (38%).

Anecdotal feedback from pharmacists is that women have appreciated being able to get trimethoprim without a prescription, and have appreciated the thoroughness of the approach.

Secondary benefit: Best practice treatment

A secondary benefit is an increased likelihood that women will receive a recommended first-line agent for cystitis rather than norfloxacin or another broad spectrum agent. This could reduce the risk of bacterial resistance to quinolone antibacterials or other broad spectrum agents. There have been

[a] NZ Girl is a social magazine aimed at women in their 20s and 30s with around 30,000 followers. The survey, conducted in December 2012, was answered by 1567 respondents.

considerable concerns about fluoroquinolone resistance in New Zealand[30] and internationally.[5,31,32] Schito, et al.[32] noted it may worsen because of clonal spread and selection of resistant mutants. These authors recommended using narrow spectrum antibiotics with limited rates of resistance instead. Avoidance of broad-spectrum agents also reduces the risk of *Clostridium difficile* infection and MRSA.[5] A related benefit is that the reclassification of nitrofurantoin would increase the number of women who receive guideline-compliant dosing and duration of treatment. [redacted] Like BPAC Guidelines,[4] SIGN Guidelines[33] also recommend short courses of antibiotics.

Patients may use left-over antibiotics (from previous doctor supply, potentially for any condition, and prescribed for other members of the family) when they cannot get to the doctor. A consultation with the pharmacist instead (who is likely to be more accessible) provides either the correct antibiotic (in the correct dose and duration) or a referral to the doctor for appropriate management, as necessary.

Secondary benefit: Health funding and the health system

A third benefit is to health funding from taxpayers. Urine cultures are considered unnecessary for uncomplicated cystitis.[4,5] BPAC held concern that unnecessary urine cultures from uncomplicated UTIs were wasting money, noting that over $12.5 million was spent on nearly 800,000 urine cultures in 2005.[34] Auckland District Health Board reports the cost of a routine urine culture as $20.70 excl. GST.[35] While it is unclear how many women with uncomplicated cystitis without complex features have a urine culture, reclassifying nitrofurantoin and therefore allowing women with antibiotic treatment in the last six months to be treated by pharmacists could save taxpayers $207,000/year for every 10,000 women treated by a pharmacist who would otherwise have had a urine culture. Taxpayers currently fund a prescribed antibiotic (and urinary alkaliniser also if prescribed), a dispensing fee ,a drug margin less any patient co-payment, together with the administration costs associated with claims payment so there are extra savings and reduced pressure on the drug bill. The health system will benefit from maximising the utilisation of the pharmacist in primary care services (see below also).

Secondary benefit: Further updating pharmacists

A fourth benefit is that pharmacists will receive a further update around urinary health, extending their knowledge further in the treatment of cystitis. This extension of knowledge will be beneficial for women with cystitis in maximising the likelihood of appropriate management, including appropriate advice and referral to the doctor. It will upskill pharmacists in their professional role (e.g. with women receiving prescribed treatments as well as non-prescription supplies). It may also be beneficial for prescribers who may be updated on latest guidelines for UTI treatment in their discussions with their local community pharmacist. Pharmacists will also be given the opportunity to be able to improve treatment for a subgroup of women entering their pharmacy seeking relief for likely cystitis, who they currently can only offer urinary alkaliniser to while they wait to see the doctor.

Secondary benefit: Relief for busy doctors

A fifth benefit will be to those doctors or A&E clinics who are particularly stretched who have one less urgent consultation to fit in. With an ageing population and pressure to expertly manage chronic diseases in an increasingly complex population, and keep patients out of hospital, pressure on primary care can only increase further. Recent initiatives to offer free doctor visits for under 13 year olds, and increasing the goal of heart health and diabetes checks to 90% of those eligible, are likely to increase

primary care workload. Furthermore, Health Workforce New Zealand identified general practice as "an area of particular need, especially in certain rural and provincial areas."[36] Anecdotally, some pharmacists have reported some general practices referring women with cystitis for pharmacist-supply of trimethoprim, showing a two-way patient-centred collaborative referral process in action. This initiative may help doctors become a little more accessible or able to spend more time and resources on complex chronic care cases if seeing less minor ailments. It is noted that the majority of UTI treatment will appropriately remain with general practice owing to the referral criteria.

Secondary benefit: New Zealand productivity

A final benefit will be to the country's productivity. Women could easily take on average 75 minutes off work to see their doctor for an appointment for their cystitis including travel, waiting and consultation time. Additional to impacting the woman, this has an impact on her employer, the New Zealand economy and on New Zealanders collectively.

Potential risk of harm to the consumer as a result of the proposed change, and factors to mitigate this risk.

In the trimethoprim model, potential harms were managed by ensuring pharmacists successfully complete training, with a 100% pass mark, before supply, and having strict criteria for supply. These strict criteria include: minimum and maximum ages; the requirement for clear symptoms to minimise the risk of misdiagnosis; checking for potential warning signs, and referral if any warning signs exist or the criteria for supply is not met. We have identified a low-risk group of women to treat by pharmacists. This subgroup represents a small minority of those with symptoms of UTIs, and excludes children, men, elderly, pregnant women, those with complicated features, those with likely treatment failure, and any with indicators of possible pyelonephritis. We have taken a very careful approach to minimise the risks to consumers.

Potential harm and the relevant risk management strategies are summarised in the appendices, and as follows:

- Likelihood of serious side effects will be minimised by: screening for contraindications and precautions; limiting the age of women eligible for treatment (elderly are excluded); using an appropriate dose that is well under the 7 mg/kg/day that is particularly toxic;[11] and providing verbal and written information to women being treated, including signs to watch for and what to do if they occur.
- Risk of misdiagnosis is minimised by pharmacist training (the training as used for trimethoprim will be mandatory) and use of the screening tool and algorithm, plus the consumer information sheet that includes warning signs (see also below). Note that the screening tool requires a very clear indication of cystitis before treatment.
- Risk of increased overall usage of antibiotics is relatively low. With only 28% of women improving within a week without treatment,[37] most women will already access antibiotics for cystitis. Some women will continue to attempt to self-treat first using home remedies such as baking soda, and large volumes of water, or urinary alkalinisers before seeking help.
- Fragmentation of care is limited by advising doctors of supplies of the antibiotic where the patient gives permission, like after hours doctors do. An in-house audit of previous vaccination services administered through 76 Green Cross Health pharmacists showed that 95% of consumers consent to their doctors being advised of the vaccine given. We would have no reason to believe this would be any different with other services such as the supply of antibiotic treatment.

- Dryden, et al.[38] suggested that doctors may move to second-line agents should trimethoprim and nitrofurantoin reclassify in the UK. However, this seems unlikely as it can be hard to change long-standing prescribing practices, even with active intervention, and New Zealand guidelines and judicious use of fluoroquinolones are still being promoted.

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

Cystitis is a lower urinary tract infection with classic symptoms of dysuria, frequent and urgent urination, suprapubic tenderness, polyuria and haematuria.[5] Lower back pain may be present.[39]

Diagnosis is primarily based on symptoms, and signs and tests for bacteria or white cells in the urine *"rarely have important implications for diagnosis"*.[5][p3] Acute uncomplicated pyelonephritis is considerably less common than cystitis.[40] Cystitis is diagnosed by symptoms – dysuria plus frequency without a history of vaginal discharge or irritation has a probability of UTI of >90%.[40]

Urine cultures are recommended where symptoms are unclear, pyelonephritis or a complicated UTI is suspected, recurrent cystitis, and treatment failure.[40] In all these cases, the patient will be referred to the doctor using the screening tool. Additionally, referral to the doctor would happen in cases of treatment failure with antibiotics or with more than three UTIs within one year.

Diagnosis is difficult in elderly patients, [5] and such patients are excluded from pharmacist-supply.

The Medicines Classification Committee reclassified trimethoprim in 2012,[1] considering that women are already accessing the pharmacy for urinary alkalinisers for cystitis, that diagnosis is based on symptoms, and that pharmacists would receive specific training and use a screening tool. The screening tool requires clear symptoms which would, according to BPAC guidelines,[4] and SIGN guidelines[5] suggest cystitis and result in antibiotic treatment with no need for a urine test. To be eligible for treatment, the woman needs to have two or more of: dysuria, urinary frequency, urinary urgency and suprapubic pain. Additionally, the woman needs have no potential signs of pyelonephritis, defined as: fever, chills, pain in sides or back, nausea, vomiting or being *"very unwell"*.

We recommend that pharmacists who have already received training for trimethoprim are able to access an update covering nitrofurantoin and providing refresher of other information from their previous training. We are not intending to mandate this, given that pharmacists have already had to successfully complete training for trimethoprim, that a screening tool and algorithm would be used, that the training update would be provided, and that there is an expectation for health professionals including pharmacists to keep themselves up-to-date. Pharmacists need to keep a portfolio of their training that can be reviewed by the New Zealand Pharmacy Council to ensure they maintain their education. It is logical for pharmacists to use this reclassification as a prompt to access the training and ensure they are appropriately trained before supply. The updated training information would include a reiteration of the need to work strictly within the screening tool, to provide written information for each supply and on the diagnostic criteria, including management of suspected pyelonephritis.

Relevant comparative data for like compounds

Currently women with uncomplicated cystitis who had antibiotic usage in the last six months but otherwise meet the criteria for trimethoprim cannot receive best practice treatment in the pharmacy. Their options are to seek medical treatment, or to make do with urinary alkalinisers or home remedies. Urinary alkalinisers may provide symptom relief, but do not cure the problem, and most of these

women are likely to ultimately need medical treatment. Methenamine hippurate is a general sales medicine, but is not considered appropriate for treatment of urinary tract infections.[41] Although cranberry products are available in the pharmacy as ongoing support for urinary health, it does not have a place in treating acute cystitis.[34]

Other antimicrobials available without a prescription in New Zealand include:

- Trimethoprim supplied to women meeting strict criteria by pharmacists who have successfully completed training
- 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 famciclovir for herpes labialis (pharmacist-only medicine)
- Oral oseltamivir for influenza (pharmacist-only supply under strict criteria)
- Topical antifungals for skin (pharmacy-only or general sales according to indication)
- Povidone iodine for skin infections and throat infections (General sales)

One of the comments expressed in 2012 when the trimethoprim reclassification was considered was that nitrofurantoin was a more suitable candidate,[42] presumably because of its low level of resistance. *E coli,* the most common cause of cystitis,[25,26] has considerably greater rates of susceptibility to nitrofurantoin than trimethoprim, according to Labtest data for Auckland (99% versus 71%),[10] and (hospital derived) data from Canterbury (99% versus 78%).[43] However, some of the minor causes of uncomplicated cystitis have increased susceptibility to trimethoprim than nitrofurantoin. See section on resistance, below.

The text, Meyler's Side Effects of Antimicrobials (2010), states that for nitrofurantoin, "drug-related adverse events ... occur in fewer patients than with co-trimoxazole or trimethoprim, for example."[44] Medsafe's Suspected Medicine Adverse Reaction Search (SMARS) database for nitrofurantoin (1 Jan 2000 to late 2014) held 129 reports with 260 reactions and two deaths. The SMARS database for trimethoprim (including co-trimoxazole) for the same dates held 431 reports covering 822 reactions and three deaths. Trimethoprim is used considerably more often than nitrofurantoin, but nitrofurantoin has the concerning chronic pulmonary side effects that are in many of the reports for nitrofurantoin. Anaphylaxis, skin rash, and hepatic effects were reported with both medicines. An acute pulmonary reaction occurs with nitrofurantoin and is discussed further below.

Local data or special considerations relating to New Zealand

Local data is discussed throughout this application, particularly under resistance and local guidelines for treatment of cystitis. New Zealand data collected on pharmacy management and prescribed treatment for women with UTIs prior to the reclassification (baseline) is awaiting publication and will be provided in confidence separately.

The current BPAC guidelines are for trimethoprim and nitrofurantoin as first-line agents for uncomplicated cystitis.[4] This may change over time, and if so, this reclassification would be reviewed.

Chlamydia trachomatis is a common condition in sexually active people in New Zealand, occurring in around 5% of pregnant women, 2% of sexually active secondary school students and 3% of women attending a university health clinic.[45] Being usually asymptomatic, it should be considered in people with a UTI who are at risk of STIs. The original training for trimethoprim included screening for risk factors (e.g. irregular use of condoms, previous STI)[45] and referral for a STI check as appropriate. Chlamydia screening and treatment through pharmacy occurs in the UK, and an obstetrician and

gynaecologist specialist suggested that this could be worthy of consideration here in the future. Training for pharmacists will also include other STIs. The screening tool specifically questions about vaginal symptoms as these can indicate an STI. It is important to note that Pharmacists already have this discussion with women where appropriate around the supply of Emergency Contraceptive Pill, with trimethoprim and with vaginal antifungal provision.

Interactions with other medicines

Nitrofurantoin has fewer drug interactions than trimethoprim.

Antacids containing magnesium trisilicate should be avoided at the same time as nitrofurantoin owing to possible impaired absorption.[46] This antacid is uncommon but pharmacist training and the patient information sheet will mention this interaction.

Uricosuric drugs such as probenecid and sulphinpyrazone can interact through inhibiting renal tubular secretion of nitrofurantoin and thus increase potential toxicity and reduce nitrofurantoin concentration in the urine, potentially affecting its efficiency.[46] Stockley's Drug Interactions notes this as theoretical. Training and the patient information sheet will mention this interaction.

Stockley's Drug Interactions reports that diphenoxylate and antimuscarinic drugs such as propantheline can double the absorption of nitrofurantoin in some patients, but that no reports have arisen of problems from concurrent use.

Stockley's warns of an important interaction with clozapine with other drugs well known to cause agranulocytosis, but there is only one case with nitrofurantoin.[47] Given the potential importance of this reaction, referral to the doctor will be recommended in this case.

Urinary alkalinisers can make nitrofurantoin less active,[5] and so avoidance will be advised.

Contraindications and precautions

Nitrofurantoin lacks efficacy in systemic sepsis or upper renal tract infections, and therefore needs to be avoided in these cases (which would require doctor referral regardless). Trimethoprim is also not recommended in these cases, and pharmacists are already screening for signals of such infection and referring if warning signs exist. Additionally, patients are warned through the information sheet of when to see the doctor.

Nitrofurantoin is contraindicated in patients with poor renal function (Creatinine clearance under 60 mL per minute) and should be avoided close to time of delivery for pregnant women.[46] Pharmacists are already referring in case of renal impairment or pregnancy. Studies in pregnant women have not shown any increase in risk of foetal abnormalities at any stage of pregnancy, and therefore use in an early, unrecognised, pregnancy should not be unreasonable.

Owing to trace amounts of nitrofurantoin in breast milk, and potential for serious adverse reactions in infants under one month,[46] pharmacists through training will be advised that trimethoprim is the preferable treatment consideration provided they have not had an antibiotic in the previous 6 months.

Nitrofurantoin is contraindicated in cases of previous hypersensitivity. This will be screened for.

Possible resistance

> *"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[48]

Furthermore, Dryden et al included in their list of "Actions to optimize antibiotic prescribing":[49]

- 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."[50]
- Select agents with a view to minimising collateral damage

Pharmacists supplying nitrofurantoin will have successfully completed training from the College of Pharmacists for urinary tract infections (the training prepared for the trimethoprim reclassification). This training covered antibiotic resistance in pre-reading, audio conference content and assessment.

Despite over 60 years of use for urinary tract infections, bacterial resistance has *"not appreciably evolved"* with nitrofurantoin.[8][p357] When used as prophylaxis, bacterial resistance remains low. Resistance remains low in countries that used nitrofurantoin extensively,[51] and in recurrent UTIs.[32]

Trimethoprim resistance for bacteria in urine samples is increased with previous trimethoprim use, (odds ratio 1.22, confidence interval 1.16-1.28), and with previous exposure to other antibiotics (odds ratio 1.18, confidence interval 1.06-1.32). [3] This effect is considerably stronger with usage 8-15 days prior to the urine sampling (probably reflecting a repeat visit following treatment failure), diminishing considerably up to the 45 day point, and lowering again in those exposed 45-120 days previously, before disappearing in those provided with trimethoprim more than 180 days previously. There is no evidence of the same effect with nitrofurantoin.

The vast majority of uncomplicated UTIs are caused by *E. coli* (70-95%), the remainder are caused by *Staphylococcus saprophyticus* (4-10%) and the rest by *Proteus*, *Pseudomonas*, *Klebsiella* and *Enterobacter* species.[25,26,32] Infection is usually monomicrobial.[32] A study in general practice in Canterbury, New Zealand , conducted in 2001-2002 tested bacterial resistance in urine from women aged 16-50 years with symptoms of cystitis and meeting criteria for significant infection. Most (81%) were *E. coli*, 13% were *S. saprophyticus*, and 6% were other organisms (*Enterobacter cloaecae*, *Klebsiella pneumonia*, *Proteus mirabilis* and *Steptococcus agalactiae* (gp B)).[52] See the appendices for the susceptibility profile for these bacteria with trimethoprim and nitrofurantoin from Labtest data (2013) in Auckland.[10] This data includes complicated infections, suspected pyelonephritis and treatment failure as well as an unknown proportion of uncomplicated cystitis in the population group we are targeting. *E coli* and *S. saprophyticus* are more likely to be susceptible to nitrofurantoin than trimethoprim, but some of the minor causes (e.g. *K. pneumoniae* and *P. mirabilis*) have a higher susceptibility for trimethoprim than nitrofurantoin, and *Pseudomonas aeruginosa* is always resistant to both trimethoprim and nitrofurantoin. While reflecting a limited number of urine samples, the aforementioned Canterbury study by Mangin, Toop and others,[52] found that across all organisms the bacterial resistance to trimethoprim occurred in 15% (95% confidence intervals 9-24%) while

resistance to nitrofurantoin occurred in 3% (1-8%). For *E.coli* the corresponding figures were 18% for trimethoprim and 0% for nitrofurantoin.

A UK survey from 2003 found that 4.5% of households had a leftover antibacterial drug, kept in case of future need, and 2.4% of households had standby antimicrobials.[53] Courses of medicine over six days were significantly more likely to be kept as leftovers than short courses (three days). The authors suggested the standard duration of treatment be shortened to 3 to 5 days to reduce the temptation to keep excess, particularly given that repeated courses with the antimicrobials increase risk of colonisation and infection with drug-resistant organisms. They also recommended reinforcing the message that these drugs should only be taken after the advice of a health professional. Leftover and standby drugs mean people may not only use repeated doses of drugs they may have resistance to, but also that they may be using them without clear symptoms of cystitis, with possible warning symptoms, and (for leftover drugs) for insufficient duration, all of which are inappropriate practices for good antimicrobial stewardship.

Trimethoprim resistance was higher with more prescriptions in the previous 12 months, with three or more prescriptions in the last 12 months having an odds ratio for resistance of 7.5 (CI 2.7-20.9), while one or two prescriptions in the last 12 months approximately doubled the risk of resistance. Resistance was higher with more recent use of trimethoprim than with earlier use. Resistance was seen in 44% of the 25 patients who had taken trimethoprim in the two to three months prior, in in 20% of 44 who had taken trimethoprim four to six months prior, and in 35% of the 26 who had taken trimethoprim 7-9 months prior and 25% of the 20 who had taken trimethoprim 10-12 months prior, versus 20% of the 480 people with no trimethoprim in the last 12 months.

Nitrofurantoin became the only antimicrobial agent of first choice in UTIs in 2005 in the Netherlands owing to decreasing susceptibility of bacteria to trimethoprim.[7] A study through general practice found that nitrofurantoin was used in 66% of women aged 11 years or older with UTIs in 2009 versus 58% in 2004. Yet the overall susceptibility of *E.coli* to nitrofurantoin was 100% in 2009, little changed from 99% in 2004.

To summarise, nitrofurantoin is an ideal agent for reclassification for cystitis. Such a reclassification would encourage use of a first-line agent. Use in women who have had antibiotic usage in the last six months is appropriate given the nature of bacterial resistance associated with this medicine. The screening tool is robust and pharmacists are aware of antimicrobial resistance issues.

Adverse events – nature, frequency, etc

Guay's review of nitrofurans in Drugs reported that "short term nitrofurantoin therapy is a reasonably well-tolerated treatment for UTI".[8][p361]

In a hospital based study from 1971 in which a nurse ascertained side effect information each day in patients (children and adults) taking one of three prescribed antibiotics, 9.2% of 757 patients reported side effects with nitrofurantoin.[11] Notably, in this observational study, a dose related effect appeared, as did a highly significant effect of patient weight, with 14.5% of adults under 120 pounds (54kg) reporting non-allergic adverse events versus 2.6% of adults over 150 pounds (68kg). The most common effects were gastro-intestinal in nature, primarily anorexia, nausea or vomiting. There were 15 reports of dermatological reactions (1.9% if no patient reported more than one dermatological reaction), and 13 haematologic reactions. No cases of hepatitis occurred, but two of pulmonary infiltration did. Most side effects were classed as mild, with one severe reaction to nitrofurantoin. The

authors noted that doses in earlier studies that gave adverse event frequency data were higher than those in use at the time of this study. Furthermore, approximately one third of patients taking nitrofurantoin in this study were taking 300 mg or more per day, a higher dose than currently recommended in New Zealand according to BPAC guidelines.[4] Thus, adverse event data on nitrofurantoin needs to be treated with caution depending on the study period and likely dosage; some old data may be quoted without such consideration. It is also noted that the study patients were hospitalised, and therefore probably considerably different from a population using pharmacy or general practice for treatment of cystitis. These authors noted that the toxicity was particularly high (23.6% had non-allergic adverse events) at a dose of 7 mg/kg/day. For a 50 kg woman that represents a daily dose of 350 mg. Substantially fewer (1.6%) patients receiving less than 4 mg/kg/day had non-allergic adverse events. A 50 kg woman taking a dose of 200 mg/day would receive 4 mg/kg/day. These authors believed the nausea and vomiting to be centrally mediated rather than owing to local irritation given the dosing effects and their experience with ingestion with food or the slow release product and the occurrence of nausea and vomiting after intravenous injection.

In 1982, Penn and Griffin reported that the UK recommended dose was 100 mg four times daily for two weeks, while the recommended dose in Sweden was 50 mg three or four times daily for up to two to three weeks.[54] This differs from the BPAC recommendation of 50 mg four times daily for five days as we have used.

Peripheral neuropathy occurred more commonly in spontaneous adverse reaction reports in the UK than in Sweden or the Netherlands, possibly reflecting the higher daily dose recommended in the UK compared with Sweden.[54] The UK reported 64 reports from 1964 to 1980, while Sweden (1966-76) and the Netherlands (1975-80) reported 20 and 8, respectively.

Sixty four reports of acute lung reaction (14% of all nitrofurantoin reports) were received in the UK (1964-80) comprising 48 pulmonary reports and 16 of bronchoconstriction.[54] This was of a base of 265,000 prescriptions per year in 1976. In Sweden 398 acute lung reaction reports (43% of all nitrofurantoin reports) occurred between 1966 and 1976, while in the Netherlands 11 reports (12% of all nitrofurantoin reports) occurred from 1975-1980.

Eleven cases of fatalities with nitrofurantoin were reported in Sweden in 1966-1976.[55] Six cases were long term use (three months to nine years). All patients affected were aged 64 years or over.

We consider that the primary adverse reaction of concern for nitrofurantoin usage for UTIs is for acute pulmonary reaction. Acute pneumonitis typically presents similar to a respiratory infection and may or may not have pulmonary oedema and pleuritic chest pain.[8] This is believed to be a hypersensitivity reaction occurring very rarely[15] and more common in the elderly.[8,15] Onset is from several hours to eight to ten days after initiating therapy.[8] Resolution occurs rapidly after discontinuing nitrofurantoin, frequently within a day, and 88% are resolved in three days.[15] If this reaction has occurred previously, future use must be avoided as a stronger reaction would result.[8] Thus the key issue is ensuring women receiving the treatment are screened for previous problems with antibiotics that they are well-informed about the possible reaction including what to do if it occurs, and that any such suspected reaction is reported to their doctor and CARM. Information for pharmacists and patients will highlight these issues, and impress upon the pharmacist the importance of keeping the GP informed (with consent of the woman being treated).

The more dangerous version of nitrofurantoin-induced lung disease is the chronic version. Although less frequent than the acute form, it was the chronic form that was the primary focus in Prescriber Updates in 2002,[14] 2006,[13] and 2012[12]. This form occurs more commonly in older women, possibly

because they are more likely to be on preventative therapy. The greatest difficulty is that chronic pulmonary disease can be insidious in onset, particularly given the patient may be elderly with comorbidities, the prescriber may have low awareness of nitrofurantoin toxicity, and the effect may vary clinically.[14] Therefore cough and shortness of breath may not initially be identified as nitrofurantoin toxicity. With a delay in diagnosis, lung damage may be irreversible and fatal. Guay reported a fatal outcome in 8-10% of patients from respiratory failure.[8]

It is important to note that the acute and chronic pulmonary reactions are considered to be different. The acute reaction is considered to be a hypersensitivity, while the chronic is thought to occur through ongoing toxicity.

Other potentially serious rare drug reactions with nitrofurantoin include hepatic effects, neurological and haematological. See SMARS data in the appendices for further details on New Zealand reactions. Serious reactions are increased in patients with renal impairment, and the New Zealand datasheet notes a contraindication in people with creatinine clearance less than 60 mL/min. However, this is more conservative than in the UK where the contraindication has recently been updated by the MHRA following a review of evidence to an estimated glomerular filtration rate (eGFR) of 45 mL/min/1.73m^2, with a note that a short course can be used cautiously in cases of multidrug resistant pathogens and an eGFR of 30-44 mL/min/1.73m^2 where the benefits are considered to outweigh the risks.[56] Any woman with known renal impairment will be referred under our screening tool, as they currently are for trimethoprim. However, The MHRA information suggests that the New Zealand datasheet is unnecessarily restrictive.

Potential for abuse or misuse

There is no known potential for abuse of this medicine. Misuse is also unlikely. With trimethoprim having only three tablets there is limited opportunity for keeping left-over medicine for a further occurrence. With nitrofurantoin 20 tablets (five days) has greater opportunity for this occurrence, but still limited compared with prescribing behaviour which is sometimes for seven days' supply. Should this happen, it is not ideal, but is better than self-treating with an antibacterial which has higher levels of bacterial resistance and is affected by use of antibiotics in the last six months (as is the case for trimethoprim).

Other

Details of consultation conducted and comments made will be provided to the committee with the finalised screening tool when the last consultation is completed. This application has had medical review.

Integrated care is important with this medicine and this therapeutic area. Therefore, the expectation will be that the doctor will be informed of the supply unless the woman does not consent to this action. Pharmacists will be encouraging such notification. The information sheet will tell the woman the name of the medicine and that if her condition does not improve or recurs to see a doctor and tell the doctor she has been taking nitrofurantoin. The pharmacist will cover this verbally as well. Should the pharmacist believe the woman is at risk of an STI, should the diagnosis be in doubt, or should the woman not otherwise fit the criteria for supply, she will be advised to see her doctor. If the woman has an allergic reaction she will be encouraged to report it to her doctor, will be given written information about it to keep and CARM will be informed. We anticipate that some doctors and practice nurses will continue to refer women with uncomplicated cystitis to the pharmacy for treatment.

Summary

This application to reclassify nitrofurantoin for uncomplicated cystitis in a sub-group of women appropriate for such treatment will benefit women who cannot currently be treated for this infection owing to recent antibiotic use. Women who have been able to access trimethoprim have reportedly been grateful for being able to access this medicine in a timely manner, but those with recent antibiotic use have missed out. Nitrofurantoin will therefore provide a safe and useful addition for the treatment of women with cystitis. We have taken a cautious approach to maximise benefits for women and minimise risks such as adverse reactions and antibiotic resistance.

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