Health and Disability Commissioner
Te Toihau Hauora, Hauātanga

A Decision by the Deputy Health and Disability Commissioner

(Case 20HDC01462)

Introduction

1. The Health and Disability Commissioner received a complaint from Mrs A about the services provided to her husband, Mr A, by several healthcare providers, including rehabilitation specialist Dr B at a spinal unit (part of what was then a district health board (DHB),[1] a medical centre, GP Dr C, a pharmacy, and the Urology Department at a public hospital in another region. In particular, the complaint concerns the failure to inform Mr A about the rare but serious risks associated with using the antibiotic nitrofurantoin for longer than six months, in particular the risk of pulmonary fibrosis.[2]

2. This report is the opinion of Carolyn Cooper, Deputy Health and Disability Commissioner, and is made in accordance with the power delegated to her by the Commissioner.

3. Mr A was diagnosed with pulmonary fibrosis as a result of the long-term use of nitrofurantoin, and consequently he passed away in 2019. My deepest condolences to Mrs A for her loss. In her complaint to HDC, Mrs A said: 'Above all I would like to prevent another avoidable death as a result of a lack of professional knowledge about the adverse effects of nitrofurantoin.'

[1] Now Health New Zealand|Te Whatu Ora (Health NZ).
[2] Scarring of the lung tissue over time.

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4. Mr A took nitrofurantoin[3] for about 28 months between 2017 and 2019 but was not made aware of the known risk of pulmonary disease from long-term use of the medication. Had he been informed he could have made an informed choice about whether to continue taking nitrofurantoin. Several health professionals missed opportunities to ensure that he was made aware of the risk, and they share responsibility for this. Some practitioners were not aware of the risk themselves, and some presumed that other clinicians had informed Mr A about the relevant risks at appropriate times.

5. Although I am very critical that none of the health service providers who cared for Mr A ensured that he understood the risks, I consider that no single individual or service was significantly more responsible. Clearly, several providers failed Mr A.

6. Mrs A's complaint has shone a light on a very important issue and has prompted necessary improvements and education to reduce the chances of a similar situation. Some improvements have occurred already, and my recommendations for further actions are noted at the end of this report.

Background and information gathered

7. Mr A was paraplegic (following an accident many years previously) and had a neurogenic bladder,[4] which he managed with intermittent self-catheterisation (ISC). On 5 July 2017, specialist Dr B noted that Mr A was experiencing recurrent urinary tract infections (UTIs) secondary to his ISC, and he was prescribed an initial two-month course of nitrofurantoin to prevent further UTIs. The DHB told HDC that Dr B recalled having informed Mr A in July 2017 that prolonged use of nitrofurantoin carries a risk of serious lung fibrosis but acknowledged that there is no record that this occurred. Conversely, Mrs A told HDC that Dr B did not inform her husband of this risk.

8. As nitrofurantoin was effective in treating and preventing Mr A's recurrent UTIs, other providers continued to prescribe it over the coming months and years through to 2019. These providers included GP Dr C, and Dr D, a urology registrar at a public hospital in another region. The pharmacy dispensed the nitrofurantoin as prescribed.

9. According to Mrs A, at no time was her husband aware of the risk of lung disease from using nitrofurantoin for over six months. Mrs A told HDC that after having taken nitrofurantoin for about six to eight months, initially her husband developed a mild and dry cough, but as they were not aware that this could be related to the nitrofurantoin, they did not raise any concerns about this at the time.

Clinical advice

10. To investigate the care provided to Mr A, HDC obtained advice from in-house clinical advisor GP Dr David Maplesden (Appendix A), urology consultant Dr Andre Westenberg (Appendix B), and pharmacist Ms Pauline McQuoid (Appendix C). All advisors agree that when the use of nitrofurantoin exceeded six months, Mr A should have been told about the potential long-

[3] There were only two breaks in treatment, totalling five months when he was not taking nitrofurantoin.
[4] Lack of bladder control due to a spinal cord or nerve problem.

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term risks so that he could make an informed decision about whether the benefits of continuing the nitrofurantoin outweighed the risks. The advisors were all mildly to moderately critical of the omission. However, this case has highlighted that many practitioners who prescribe and dispense nitrofurantoin, including those who treated Mr A, were not aware themselves of the potential for serious lung damage from long-term use beyond six months.

11. Dr Maplesden, who advised on Dr C's role in Mr A's care, noted that the rare risk of serious pulmonary side effects associated with the use of nitrofurantoin have been published by Medsafe since 2002. In a 2012 update for prescribers, Medsafe provided the following key messages associated with prescribing nitrofurantoin:[5]

- Nitrofurantoin treatment should not be prescribed beyond six months unless the benefits outweigh the risks.
- Patients receiving long-term nitrofurantoin treatment should be monitored for changes in pulmonary function.
- Nitrofurantoin treatment should be discontinued at the first sign of pulmonary damage.

12. Dr C told HDC that at the time he was not aware of the risk of pulmonary damage from long-term nitrofurantoin use. Dr Maplesden acknowledged the difficulty in clinicians keeping abreast of all clinical updates and education regarding medication. However, he advised that nevertheless Dr C had a duty to be familiar with the potential risks and monitoring requirements of medication he prescribed, which for nitrofurantoin included a risk of pulmonary toxicity from long-term use. Dr Maplesden said:

> 'Certainly, once [Dr C] decided to extend the course of nitrofurantoin beyond six months … I believe such discussion [with Mr A about the risk of lung disease] should have been undertaken.'

13. Dr Maplesden was moderately critical that Dr C prescribed prolonged courses of nitrofurantoin without making himself aware of the associated potential risks and monitoring requirements. Dr Maplesden commented that responses to this complaint indicate that this may not have been well recognised in primary care at the time. He said:

> 'This might relate in part to the limited occasions on which a GP might consider prescribing long-term prophylactic[6] nitrofurantoin, the rarity of the adverse effect, the multiplicity of sources GPs use to remain updated on clinical issues and the time required to remain abreast of all relevant clinical issues and updates.'

14. Dr C told HDC: 'Had I been aware of the serious long term side effects of this medication, I would have certainly performed a risk/benefit analysis.'

[5] Dr Maplesden also noted that similar information 'has been provided by Medsafe and BPAC [Best Practice Advocacy Centre] on several occasions over at least the past 18 years, and precautions [have featured] in relevant local HealthPathways'.
[6] To prevent disease.

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15. In relation to Mr A's prescription of nitrofurantoin in March 2018 by urology registrar Dr D, my independent advisor, Dr Westenberg, advised:

> 'Nitrofurantoin is widely used as prophylaxis against urinary infections. The complication of pulmonary fibrosis is rare and if one had never come across anyone who had suffered it, it would not be at the front of one's mind. Both the pharmacist involved in this case and the GP, [Dr C], were not aware of the association, and neither were most of their colleagues. It appears that [Dr D] was also unaware of the association.'

16. Dr Westenberg considered that given that the nitrofurantoin was prescribed by several clinicians, and neither Dr B, Dr C, Dr D, nor the pharmacy dispensers ensured that Mr A understood the very rare risk of pulmonary fibrosis, the omission by urology registrar Dr D was by itself a relatively minor departure from the standard of care.

17. In response to the provisional opinion, Dr D told HDC that in his clinical letter of 21 March 2018, he endorsed the ongoing use of nitrofurantoin as prophylaxis without a qualifying statement to highlight the potential adverse effects to Dr C or Mr A, and he did not document a discussion with Mr A about the risks of nitrofurantoin.

18. Dr D told HDC that given the knowledge he has since acquired, he can look back on his consultation with Mr A with a degree of criticism, but this is tempered by his knowledge of the nature of his role in a Urology Department — ie, undertaking an unsupervised procedural clinic where time and space being allocated to more in-depth clinical discussions and the senior support to facilitate these discussions was limited.

19. Dr D also said:

> 'These oversights are difficult for me to accept, however they are tempered by the fact I was not the doctor who had initiated the prophylaxis regimen using nitrofurantoin, and also my knowledge that the patient was under the ongoing care of a urologist in private practice in [another region].'

20. My pharmacy advisor, Ms McQuoid, advised that the pharmacy departed from the accepted standard for its omission to inform Mr A of the risk discussed above, but she believes there would not be consensus across the pharmacy profession. She stated:

> 'It is likely that many community pharmacists would view [the omission to ensure that Mr A was aware of the long-term risks of nitrofurantoin] as an unfortunate but inevitable consequence of time and cost pressures in that sector.'

21. The pharmacy told HDC:

> 'As a community pharmacist, you have to trust that the prescriber has made a conscious choice to start a patient on long-term nitrofurantoin after assessing the risks and benefits, especially if they have been taking multiple short courses of it.'

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22. In relation to this comment, Ms McQuoid said:

> 'I can understand this stance but as pharmacists we well know that prescribers don't know everything about medicines and part of our professional responsibility is to bring information to the prescriber's attention to ensure that the prescriber has all the information they need to prescribe safely. Pharmacists do this every day across NZ.
>
> …
>
> In [Mr A's] case, one of the contributory factors was multiple prescribers … Multiple prescribers and prescribing across care settings are two well-recognised risks for medication error.'

23. My advisors suggested actions that can be taken to ensure that the necessary improvements are made to the system and practitioners' knowledge about the risks of long-term nitrofurantoin. I have considered these in making my recommendations below.

24. All the practitioners who were involved in the prescribing and dispensing of nitrofurantoin to Mr A expressed their sincere condolences.

Responses to provisional opinion

25. Mrs A, Dr C, Dr D, Dr B, the medical centre, the pharmacy, and Health NZ were given the opportunity to respond to the provisional opinion.

26. Mrs A did not comment on my provisional opinion.

27. The medical centre confirmed that it had no further comments on the provisional opinion and proposed course of action.

28. The pharmacy's response has been incorporated into this report where appropriate.

29. Dr C responded to the provisional opinion expressing his condolences to Mrs A. He outlined to HDC the learnings and changes he has made to his clinical practice since the events.

30. Dr B responded that he did not wish to make any further comments and that he supports the recommendations made.

31. Health NZ's response has been incorporated into this report where appropriate.

32. Dr D provided HDC with an extensive response to the provisional opinion and expressed his condolences to Mrs A and the family for the loss of Mr A. Dr D stated:

> 'I was devastated to hear of [Mr A's] death. Any role I played in this process profoundly disappoints me. I feel a sense of responsibility for this and am immensely frustrated that my interaction with him wasn't the small moment that was needed to alter his trajectory away from premature death.

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> To [Mrs A] and other members of [Mr A's] whānau I extend my sincerest condolences for their loss and apologies for my failure to meet their expectations upon me as a clinician involved in his care. My hope is that, although this apology comes nearly six years after my interaction with him, it does not lighten the importance of it. I see my consultation with him as an opportunity missed to avoid the catastrophic side effects he encountered and my apology is genuine and emphatic.'

33. I commend Dr D for his incisive reflections. Dr D's response has been incorporated into this report where appropriate.

Opinion

34. Several providers failed Mr A by not ensuring that he understood the rare but serious risk of pulmonary fibrosis associated with using nitrofurantoin for longer than six months. As a result, Mr A was unable to make a fully informed decision about whether the potential benefits of continuing to use nitrofurantoin outweighed the risks.

35. Dr C was Mr A's GP and had a high level of responsibility for ensuring that Mr A was aware of the relevant risks of the medication being prescribed. I am concerned that Dr C himself was unaware of the risk of pulmonary toxicity associated with the long-term use of nitrofurantoin. However, although Dr C was the main prescriber, I also have concerns about the role of other providers, including Dr D, who also prescribed, and the pharmacy, who dispensed nitrofurantoin to Mr A, and could have done more to ensure that the long-term risks had been considered and discussed with Mr A appropriately. I note that while Dr B recalls telling Mr A about the risk, there is no documentation corroborating this. Further, Mrs A does not recollect Mr A being made aware of the risks by Dr B. On the balance of probabilities, I consider that Dr B did not inform Mr A of the risk. However, as the initial prescription by Dr B was for only two months, I consider that the requirement to inform Mr A of the risk of pulmonary toxicity associated with the prolonged use of nitrofurantoin would have been considerably less than for those clinicians who were involved in the prescribing and dispensing of nitrofurantoin when Mr A's use was approaching and then exceeding the six-month mark.

36. I am not critical of the medical centre, as there is nothing to suggest that any deficiency in the practice's systems contributed to Dr C's lack of knowledge about the relevant risk, which led to his failure to advise Mr A appropriately.

37. Sadly, Mr A suffered severe pulmonary damage from his long-term use of nitrofurantoin. All the healthcare providers who had a role in the prescribing and dispensing of nitrofurantoin to Mr A, particularly from around mid-2018, could have checked whether he was aware of the long-term risk at appropriate times, and it is concerning that this did not occur. The responsibility for this failing rests with several practitioners, as discussed above. I acknowledge the factors that may have contributed to the error, as raised by those involved and by my advisors, which has served to highlight the widespread improvements and education needed to prevent this from happening again.

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38. In concluding this investigation, I acknowledge and support Mrs A's wish to prevent any further avoidable deaths that may be due to the adverse effects of nitrofurantoin. The changes made as a result of Mrs A's complaint and this investigation, and my further recommendations for improvement, are discussed below.

Changes made

39. In recognition of the seriousness of this case, the providers involved have made several changes and improvements, as follows.

Medical centre

- 'When [the medical centre] became aware of the complaint and what had occurred, it engaged [a pharmacist] to undertake an audit of all patients of [the medical centre] who were being prescribed nitrofurantoin (regularly or for frequent intermittent courses over the past 12 months). As advised, [the medical centre] identified four patients that would require close monitoring.'
- 'The audit and the complaint were formally addressed at a clinical meeting on 25 August 2020 … The prospective risks and benefits of nitrofurantoin, and monitoring requirements were discussed. The clinicians with patients prescribed nitrofurantoin were asked to contact the patients and to reiterate the potential side effects of the medication and "red flags" that would prompt a requirement for review. [Mr A's] case was also discussed on an anonymous basis within the Peer Groups of some of the clinicians at the Centre — to prompt further learning.'
- 'In addition to the audit and further education provided, the Centre plans to intermittently raise the complaint and HDC investigation at clinical meetings in the future, to reinforce clinicians' obligations to ensure they have an appropriate knowledge base for the prescriptions they issue, and where they don't to access guidance in place or seek support. The first of these reiterations took place with clinical staff on 12 October 2021.'

Dr C

- 'I have made radical changes to my prescribing practice since the above incident including providing written information from the NZF[7] for all long term medications for patients and discussing the pertinent side effects with them.'
- 'I have discussed this case at two peer review meetings and noted many of the GPs that attended were also unaware about the long term pulmonary and hepatic toxicity of this medication. This has provided an important learning opportunity not only for myself, but also for my colleagues.'

[7] New Zealand Formulary — an independent resource providing healthcare professionals with clinically validated medicines information and guidance on best practice.

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Pharmacy

- 'Before this incident, I [pharmacy owner] was not aware of the particular risk associated with long term use. When we initially discussed this as a team, I found that some of our pharmacists are aware of the rare adverse effect associated with long-term use of nitrofurantoin … Other pharmacists did not know this … [A]ll our pharmacists are now acutely aware of this risk. In an effort to make more pharmacists aware of this risk, I will contact the Pharmacy Defence Association (PDA) about this case to request that PDA disseminates information to all community pharmacists about this rare adverse effect and that the risks may outweigh benefits with the long term use of nitrofurantoin.'

  In response to the provisional opinion, the pharmacy provided evidence that PDA disseminated this information in November 2020.

- 'I have also subscribed [the pharmacy] to the "Prescriber Update" bulletins put out by Medsafe to ensure that we are up to date with the latest information on medicine safety. It is my understanding that currently Medsafe send these updates to GP practices only. Other health professionals need to subscribe individually if they want to receive them.'

- 'In light of this case we have notified the prescribers for the [five patients identified who use nitrofurantoin on an ongoing basis or with frequent intermittent use over the previous six months] to alert them of the Medsafe prescriber updates: June 2012 "Nitrofurantoin — do benefits outweigh the risk long-term?" and March 2020 "Spotlight on nitrofurantoin" … [W]e will provide the prescribers of the [patients noted above] with an anonymised version of [Mr A's] case in good faith.'

DHB (now Health NZ)

- In response to the provisional opinion, the spinal unit told HDC that it investigated methods to contact the GPs of 1200 Spinal Cord injured patients from the spinal unit's catchment area, to highlight the side effects of nitrofurantoin, including pneumonitis and pulmonary fibrosis. However, the spinal unit found that this originally proposed preventative action is not possible given the current systems limitations. The spinal unit stated:

  > 'Short of going through each patient record by hand and pulling their GP details, it is not possible to create a list of our Spinal Cord Injury patients GPs.'

  Instead, the spinal unit will create an information document to be shared via the RNZCGP, with a wider reach.

  In addition, having discovered the difficulties in bulk contacting patients' GPs, the spinal unit is reviewing the configuration of its patient management system to facilitate this in the future.

- 'We have researched and sought senior pharmacist advice to ensure that [the] Health Pathways and Community Pathways reflect the risks of long-term use.'

- '[Mr A's] anonymised case was presented to [the] Mortality and Morbidity [group meeting] … on 2 September 2020, with discussion on nitrofurantoin including the risks and benefits, dosages and duration in relation to prescribing, reassessment, and monitoring.'

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Dr D

- '[A]t the time of receiving your letter on 9th November, I would have no problem recalling the relationship between nitrofurantoin and pulmonary toxicity and the potential issues this creates. More importantly I feel confident in my current ability to manage and minimise this risk: ideally by avoidance of prophylactic dosing of antibiotics altogether, failing that by avoidance of prophylactic dosing of nitrofurantoin altogether, failing that institution of "cycling" of different antibiotics. Most importantly with all nitrofurantoin prescribing by providing appropriate patient information about the relationship between long term nitrofurantoin use and pulmonary toxicity. As stated my current level of confidence is likely a result of the four years of Urology-specific training I have undertaken in the intervening time.'

40. I commend all the above actions taken by the various parties involved in Mr A's care in response to the issues identified in this case, some of which relate to an individual practitioner or service, and some of which may have a wider impact. I plan to follow up on some of these changes as appropriate to confirm their completion and outcome. In addition, I have made the recommendations and follow-up actions below.

Recommendations

Recommendation 1: Royal New Zealand College of General Practitioners and Te Tāhū Hauora|Health Quality & Safety Commission

41. I note the following advice from Dr Maplesden:

> 'I recommend [that the Royal New Zealand College of General Practitioners (RNZCGP) and Te Tāhū Hauora|Health Quality & Safety Commission] be given the opportunity to consider how awareness of the medication risks in question can be further highlighted. There may be some value in RNZCGP recommending to members a clinical audit of nitrofurantoin use to ensure those patients on long-term prophylaxis are adequately informed and are being monitored and managed in accordance with national (HealthPathways) recommendations.'

42. In light of this advice, I intend to write to the above-named organisations to forward Dr Maplesden's comment and request a response on what action they may take concerning these suggestions.

Recommendation 2: Medsafe and the Medical Protection Society

43. I note the following advice from Dr Westenberg:

> 'The risk of nitrofurantoin toxicity with prolonged courses has been highlighted in at least 2 prescriber updates published by MedSafe over the last decade. I believe a more direct approach to the urology community by means of publication of the risks of long-term nitrofurantoin in the regular Uro News updates would be worthwhile. In addition the [Medical Protection Society] case book is widely read by a range of medical practitioners and an anonymized article highlighting this particular case would provide good penetration.'

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44. In light of this advice, I intend to write to the above-named organisations to forward Dr Westenberg's comment and request a response on what action they may take concerning these suggestions.

Recommendation 3: Pharmac

45. I note the following advice from Ms McQuoid:

> 'The most reliable way to avoid this happening again is to restrict the availability of nitrofurantoin for long-term use by restricting the Pharmac subsidy beyond six months' use to "special authority"' approvals only, with specific criteria that must be met in order for the medicine to be subsidised. Whilst prescribers could still find ways around this system, it would be a way of alerting them to the risks of longer-term use.'

46. In light of this advice, I intend to write to Pharmac to request that it consider Ms McQuoid's comment and respond to HDC on any outcome of that consideration.

Recommendation 4: Health NZ

47. I recommend that within four weeks of the date of this report, Health NZ:

a) Provide confirmation that it has produced a written information resource for dissemination via the RNZCGP, as intended, to highlight the side effects of nitrofurantoin, including pulmonary fibrosis, and provide advice about its safe use. Distribution of this resource is to include the second spinal unit.

b) Advise HDC whether the above action highlighted any other issues concerning appropriate discussions of the risks of long-term nitrofurantoin usage with those patients, or any other issues concerning nitrofurantoin.

c) Consider disseminating information to relevant services within Health NZ that highlights the side effects of nitrofurantoin, including pneumonitis and pulmonary fibrosis, and report to HDC on any actions taken in that regard.

Follow-up actions

48. A copy of my final report with details identifying the parties removed, except the advisors on this case, will be sent to the Medical Council of New Zealand, and it will be advised of Dr C's name.

49. A copy of my final report with details identifying the parties removed, except the advisors on this case, will be sent to Health New Zealand|Te Whatu Ora, Te Tāhū Hauora|Health Quality & Safety Commission, Pharmac, Medsafe, RNZCGP, and the Urological Society of Australia and New Zealand, and placed on the HDC website, www.hdc.org.nz, for educational purposes.

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Appendix A: In-house clinical advice from Dr David Maplesden (GP)

'Thank you for the request that I provide clinical advice in relation to the complaint from [Mrs A] about the care provided to [Mr A] by [Dr C] and various providers from [the DHB]. In preparing the advice on this case to the best of my knowledge I have no personal or professional conflict of interest. I agree to follow the Commissioner's Guidelines for Independent Advisors. I have reviewed the following information: complaint from [Mrs A]; response from [the DHB]; response from [Dr B]; [DHB] clinical notes; response from [the medical centre] and GP notes; response from [Dr C]; response and dispensing documentation from [the pharmacy]. [Mrs A] notes her husband died from complications of nitrofurantoin-related pulmonary toxicity on 19 [Month7][8]. His GP, [Dr C], had prescribed him extended courses of nitrofurantoin since 2017 but had not warned [Mr A] of the risks of pulmonary toxicity, did not undertake any monitoring for pulmonary toxicity, and failed to recognise the symptoms of pulmonary toxicity when they did occur. [Mr A's] specialist, [Dr B], who first prescribed nitrofurantoin as prophylaxis, did not warn [Mr A] of the risk of pulmonary toxicity. The DHB's urology service who were aware [Mr A] was taking nitrofurantoin long-term did not discuss risk or remind the GP of the importance of monitoring. [Mrs A] does not want other patients to be placed at risk of suffering as her husband did.

2. [Mr A] suffered a spinal injury … which left him with a T6 level paraplegia, neurogenic bladder (managed with intermittent self-catheterisation (ISC)) and neurogenic bowel. He remained under three-yearly review at [the spinal unit]. He was reviewed at [the spinal unit] on 5 July 2017 where specialist [Dr B] noted [Mr A] was experiencing recurrent urinary tract infections (UTIs) secondary to his ISC. In the clinic note to GP, [Dr B] noted: *From the bladder point of view I will give him a course of prophylactic nitrofurantoin using 50mg at night to prevent further UTIs. If recurrent UTI is still a problem after the period of prophylactic treatment, then he would require updated urodynamic studies. Current KUB and ultrasound were unremarkable.* A prescription was provided for nitrofurantoin 50mg nocte for eight weeks. The [DHB's] response states [Dr B] discussed the need to take the medication with food to reduce the risk of gastric side effects, and [Dr B's] recall is *that he had informed [Mr A] that prolonged use of nitrofurantoin carries with it a risk of serious lung fibrosis, even though it is extremely rare. Unfortunately, this conversation was not documented.*

Comment: Use of longer courses of low-dose nitrofurantoin is accepted practice for management of recurrent UTI[9]. The cited reference concluded that nitrofurantoin is effective in the prevention of UTI. Its use may be associated with increased non-severe adverse effects; severe adverse effects occur infrequently with cohort studies reporting rates of 0.02–1.5 per 1000 nitrofurantoin users. The risk of severe toxicity seems to increase with the duration of nitrofurantoin prophylaxis. The current (July 2017) Medsafe prescribing guidance for nitrofurantoin notes there are special warnings and precautions for use regarding risks associated with long-term therapy. These are discussed further in section 12

[8] Relevant months are referred to as Months 1–7 to protect privacy.
[9] Muller A et al. Nitrofurantoin's efficacy and safety as prophylaxis for urinary tract infections: a systematic review of the literature and meta-analysis of controlled trials. Clin Microbiol Infect 2017;23:355–362

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but state that duration of long-term prophylaxis is up to 6 months and long-term therapy should be continued beyond 6 months only when the benefits clearly outweigh the risks. The need for close monitoring of pulmonary function and periodic monitoring of liver function in patients on prolonged courses of nitrofurantoin is recommended. These recommendations have been discussed in the MPS "Casebook" publication and are summarised in section 15. [Dr B's] intention was for a two-month course of antibiotic prophylaxis and further investigations should [Mr A's] recurrent UTIs continue after this. Noting the intended duration and dose of nitrofurantoin, and the statement that the rare risk of pulmonary toxicity is likely to have been discussed, I believe [Dr B's] management of [Mr A] was consistent with accepted practice. Best practice is to document any clinical information discussed at the time of the consultation but in my experience, it is not common practice to detail the potential adverse effects discussed. There is no specialist restriction on prescribing of nitrofurantoin for UTI prophylaxis and I would regard such management as within the expertise expected of GPs, and there is local guidance available for GPs in this regard (see section 14). In this context, I do not believe there was a requirement for [Dr B] to specify conditions on further prescribing of antibiotic prophylaxis if that was to occur although in the future such prescribing advice might be an additional "safety-net" to avoid the tragic outcome experienced by [Mr A].

3. The [spinal unit's] letter was received at [the medical centre] on 21 July 2017 and filed by [Dr C]. [Mr A] would have completed his two-month course of nitrofurantoin in early September 2017. [Mr A] next attended [the medical centre] on 10 August 2017 for a routine prostate check (provider [initials]). On 6 November 2017 he attended [Dr C] with symptoms of UTI for which he had begun antibiotic treatment at home. Prescription was provided for a one-week course of nitrofurantoin at treatment dose of 50mg qid then three months of prophylaxis at 50mg nocte. On 22 December 2017 [Mr A] presented to [Dr C] with symptoms suggestive of UTI. Management was discussed with the urology registrar who recommended referral for scan and cystoscopy to exclude renal tract stones and referral was made. A treatment course of nitrofurantoin was provided (50mg qid x 1 week). Pharmacy records indicate this prescription had two repeats (treatment courses) which were dispensed on 31 January 2018 and 6 March 2018, presumably for recurrent UTI symptoms.

Comment: [Dr B's] report had recommended urology referral for urodynamic studies if [Mr A] experienced recurrent UTI following the initial prophylaxis course of antibiotics. It was probably reasonable to wait and see if the November 2017 UTI was isolated or part of a pattern of recurrence prior to making the referral, and referral was undertaken when [Mr A] experienced a second UTI in December 2017. I believe it was reasonable to trial a second three-month course of nitrofurantoin as prophylaxis from November 2017 although some of my colleagues might have chosen a different antibiotic to treat the infections arising while [Mr A] was taking nitrofurantoin assuming there was a chance the infecting organism was resistant to nitrofurantoin. I note provision of "standby" treatment courses of nitrofurantoin which was reasonable given [Mr A's] situation but best practice would be to record use of these courses at the time of review. I have assumed [Mr A] was taking the nitrofurantoin as directed, and I believe it was reasonable for [Dr C] to assume [Mr A] was familiar with the adverse effects of the drug when used for prophylaxis following discussion with [Dr B] who had provided the initial prophylactic course.

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4. [Dr C] notes [Mr A] would have finished his three-month course of nitrofurantoin in early February 2018. At review on 19 March 2018 [Mr A] was well and was awaiting cystoscopy. [Dr C] has recorded *last UTI 2.5m ago* which does not necessarily correlate with the dispensing of nitrofurantoin noted above. A prescription was provided for what appears to be three stand-by treatment courses of nitrofurantoin (50mg qid x 1 week with two repeats) and these were dispensed on 19 and 26 March 2018 (one course not dispensed). If the courses dispensed on 6, 19 and 26 March 2018 were used as directed, [Mr A] would have consumed 84 x 50mg tabs of nitrofurantoin over a month. However, when reviewed by [Dr C] on 23 April 2018, notes include: *No UTI since last review* [19 March 2018]. [Dr C] prescribed a further three-month course of nitrofurantoin at 50mg nocte.

Comment: I am unable to explain the discrepancy between the dispensing of nitrofurantoin and [Mr A's] self-reporting of UTIs but I believe it was reasonable for [Dr C] to believe [Mr A's] recounting of his symptoms and to assume he had not required the "standby" courses of nitrofurantoin prescribed. On the basis of [Dr C's] notes, [Mr A] had been free of infection without apparent need for nitrofurantoin for two and a half months and the last prophylactic course of nitrofurantoin had been completed in early February 2018. It is difficult therefore to understand the clinical rationale for commencing a further three-month course of prophylaxis although had [Dr C] been aware of [Mr A's] apparent use of the treatment courses of nitrofurantoin over this period, further prophylaxis (up to six months) would have been reasonable and consistent with local guidance (see section 14). However, if [Dr C's] belief was that [Mr A] had not had any recurrence of his UTIs since completing the three-month course of nitrofurantoin in early February 2018, I believe commencement of a further three-month course of prophylaxis on 23 April 2018 was not consistent with recommended practice and I am mildly critical of this strategy.

5. [Mr A's] urological investigations were unremarkable and urology clinic letter dated 21 March 2018 noted improvement in [Mr A's] UTI issues since being on low dose nitrofurantoin (no recommendation regarding duration of therapy or precautions) with recommendation for an alternative urinary antibacterial agent to the Hiprex [Mr A] had been using for several years. [Mr A] did not attend [the medical centre] in person over the next 11 months. On 6 August 2018 [Mr A] used the patient portal to request a repeat of his "usual" medications including nitrofurantoin prophylaxis (50mg nocte x 90 tabs). The prescription was completed in [Dr C's] absence by [another GP]. On 17 October 2018 there was a further request for routine medication including prophylactic nitrofurantoin, verified on this occasion by [Dr C]. [Mr A] requested another repeat of his regular medications (nitrofurantoin not included on this occasion) [in early] 2019 (authorised by [the GP]) and was advised he would need to be seen prior to his next prescription. [Dr C] advises he did not prescribe nitrofurantoin for [Mr A] after 17 October 2018 although clinical records note he made a further prescription on 11 Month4 (see below).

Comments:
(i) [Mr A] was apparently well and free of UTIs since commencing further nitrofurantoin prophylaxis on 23 April 2018. Local recommended practice is for an initial three-month course and longer (six-month) course if there is rapid recurrence of UTI following completion of the initial course. As noted previously, I believe it was probably reasonable to prescribe

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up to six months of prophylaxis between April and October 2018 if [Mr A] had developed further UTIs on stopping the previous three-month course in February 2018, and nitrofurantoin dispensing records suggested he had developed further UTIs. However, [Dr C's] recorded impression was that [Mr A] had not had a UTI since completing the course in February 2018 and I believe it was not appropriate in that context to continue to prescribe nitrofurantoin for UTI prophylaxis. Nevertheless, I think it was reasonable for [the GP] to have assumed [Dr C] had planned a six-month course of prophylaxis when he authorised the repeat prescription of nitrofurantoin on 6 August 2018.

(ii) The risk of acute and chronic pulmonary side effects associated with use of nitrofurantoin have been published by Medsafe since at least 2002[10]. In a 2012 prescriber update[11], Medsafe provided the following key messages associated with prescribing of nitrofurantoin:

- *Nitrofurantoin treatment should not be prescribed beyond six months unless the benefits outweigh the risks.*
- *Patients receiving long-term nitrofurantoin treatment should be monitored for changes in pulmonary function.*
- *Nitrofurantoin treatment should be discontinued at the first sign of pulmonary damage.*

A 2015 BPAC article[12] included: *Serious pulmonary reactions, both acute and chronic, and which can be fatal, have been reported secondary to treatment with nitrofurantoin. The incidence of acute pulmonary reactions in patients taking nitrofurantoin is estimated to be less than 1% and it most often affects females aged 40–50 years. Acute pulmonary reactions are reported to occur more frequently after repeated courses of nitrofurantoin treatment*. The most recent Medsafe prescriber update on the subject was March 2020[13] and this emphasised the risk of pulmonary and hepatic adverse reactions increases with prolonged use of nitrofurantoin and advised: *Monitor lung and liver function regularly in patients taking prophylactic nitrofurantoin and periodically check for signs of peripheral neuropathy. Stop treatment with nitrofurantoin at the first sign of pulmonary, hepatic or neurological damage.* While this latter citation post-dates the events in question, it essentially reiterates advice present in the Medsafe data sheet for nitrofurantoin in force in 2017 (see section 12).

(iii) I am not aware of any research on awareness amongst local clinicians of the risks and monitoring requirements associated with long term use of nitrofurantoin. On reviewing the various provider responses, it appears some clinicians were aware of the risks and others (including [Dr C]) were not. Nevertheless, prescribers have a responsibility to be familiar with the potential adverse effects and monitoring requirements of the drugs they prescribe

[10] https://www.medsafe.govt.nz/profs/PUarticles/nitrofurant.htm#:~:text=First%20described%20in%201957%2C1,administrations%20for%20acute%20severe%20disease.&text=Chronic%20pulmonary%20reactions%20are%2010,less%20frequent%20than%20acute%20reactions Accessed 12 November 2020

[11] https://medsafe.govt.nz/profs/PUArticles/NitrofurantoinBenefitsOutweighRisksJune2012.htm Accessed 12 November 2020

[12] https://bpac.org.nz/BPJ/2015/October/docs/BPJ71-news-nitrofurantoin.pdf Accessed 12 November 2020

[13] https://medsafe.govt.nz/profs/PUArticles/March2020/Spotlight-nitrofurantoin.html Accessed 12 November 2020

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and to inform patients of these factors (see extracts from Medical Council of NZ statement in section 13). I believe once [Dr C] made a decision to commence [Mr A] on longer-term nitrofurantoin prophylaxis (presumably from April 2018) he should have discussed the potential hepatic and pulmonary risks associated with longer term use of the medication and had a plan in place for periodic monitoring of [Mr A's] respiratory and hepatic function. Certainly, once he decided to extend the course of nitrofurantoin beyond six months (in October 2018) I believe such discussion should have been undertaken. I am also of the opinion it is not apparent the benefits of extending the course beyond six months outweighed potential risks and there is nothing in the clinical notes or response to indicate [Dr C] considered the risk/benefit balance. I am at least moderately critical that [Dr C] prescribed [Mr A] prolonged courses of nitrofurantoin without making himself aware of the potential risks and recommended monitoring requirements of such prescribing, and therefore not undertaking recommended monitoring or discussing potential risks with [Mr A]. However, because [Dr C] was not aware of these risks, his subsequent management of [Mr A] must be reviewed in that context. I acknowledge there was no indication at this point in [Dr C's] prescribing that [Mr A] had developed a chronic pulmonary reaction to nitrofurantoin.

6. [Dr C] reviewed [Mr A] on 28 [Month1] noting he appeared well and had had no urinary infections in the last year. The most recent course of nitrofurantoin was completed about [early] 2019. On 29 [Month2] [Mr A] attended [a GP] who noted: *Monthly UTIs until about 15 months ago, went onto 12 months of nitrofurantoin 50mg od with good effect, came off three months ago* with development of UTI symptoms over the previous four days. [Mr A] had self-medicated with some leftover nitrofurantoin with improvement in his symptoms and the decision was made to complete a treatment course of nitrofurantoin then re-trial prophylaxis (50mg nocte) and review with [Dr C] in three months or before as required.

Comment: [Mr A] had apparently tolerated a 12-month course of prophylactic nitrofurantoin under the auspices of [Dr C] with no adverse effects and with a positive outcome with respect to previous recurrent UTI. He had not used nitrofurantoin for three months (per patient). Under these circumstances I believe it was reasonable for [the GP] to trial a further three-month course of prophylaxis with the assumption [Dr C] would have previously informed [Mr A] of the risks and benefits of the strategy given the history recounted.

7. On 11 [Month4] [Mr A] presented to [Dr C] with a one-week history of retrosternal pleuritic type pain and cough. An adequate respiratory history and examination is documented (lung fields clear, afebrile) and provisional diagnosis of gastro-oesophageal reflux or possibly pulmonary embolus (PE) made. D-dimer was performed and effectively excluded PE. [Mr A] was prescribed omeprazole. A further prescription was also provided for nitrofurantoin prophylaxis (90 x 50mg tabs) and this was dispensed the same day.

Comment: The rationale for providing a further prescription of nitrofurantoin is not evident from the clinical notes but I have assumed there was an intention to extend the prophylaxis period to at least six months and the prescription was provided early for convenience. If there was an intention to extend the course beyond six months, I would reiterate the

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comments previously applied to that strategy. My subsequent comments on management of [Mr A's] respiratory symptoms are made with the knowledge [Dr C] was not aware of the potential respiratory adverse effects associated with nitrofurantoin use and therefore did not recognise [Mr A's] symptoms as representing possible drug toxicity. As previously discussed, I am at least moderately critical of this omission and I acknowledge the impact this will have had on [Mr A's] subsequent management, with recommended management of patients with suspected pulmonary reaction to nitrofurantoin being immediate cessation of the drug, and severity of chronic toxicity increasing the longer exposure to the drug continues after development of symptoms. However, without this knowledge, and with the apparent reassurance [Mr A] had previously used the drug for an extended period without issues, I understand [Dr C's] failure to diagnose [Mr A's] pulmonary toxicity and to manage this appropriately. In this context, I believe [Dr C's] assessment and management of [Mr A's] respiratory symptoms on 11 [Month4] was reasonable. In hindsight, the symptoms shown by [Mr A] on this occasion were not classic for either acute or chronic nitrofurantoin-related pulmonary toxicity.

8. [Mr A] re-presented to [Dr C] on 19 [Month4] with ongoing symptoms similar to his initial presentation. He was afebrile with clear lung fields. He denied shortness of breath, haemoptysis or wheeze. Impression was *??viral tracheitis* and short course prednisone prescribed with chest X-ray ordered. Pericarditis was considered in the differential but ECG deferred until chest X-ray result was received. Chest X-ray 19 [Month4] reported no abnormality in the lungfields. On 26 [Month4] [Dr C] provided a further short course of prednisone per the patient portal (no clinical notes associated with the prescription). On 8 [Month5] [Mr A] presented to [Dr C] with *sore throat and headache for 1m … pain on swallowing, no cough, not feverish …* On examination large submandibular nodes were noted and [Dr C] diagnosed *oropharyngeal infection with lymphadenitis* and prescribed paracetamol and Augmentin with follow up per phone in a few days. Blood tests performed on 9 [Month5] showed unremarkable CBC, mild elevation in CRP (23 mg/L) and elevated ALT. On 22 [Month5] [Dr C] reviewed [Mr A] because of persistent chest pain associated with deep inspiration, headaches and slight cough but *no sputum, no wheeze, no SOB.* Cardiorespiratory assessment was normal (lung fields clear, oxygen saturations 94–96%, respiratory rate normal) and [Dr C] discussed [Mr A's] case with the respiratory registrar noting: *They are happy all major pathologies have been eliminated. They recommend treating symptomatically only.* ECG was performed (no acute changes) and provisional diagnosis of viral pleurodynia recorded. Blood tests showed normal CRP and CBC and treatment was provided with Naproxen.

Comment: Leaving aside the issue previously discussed regarding [Dr C's] knowledge gap leading to delayed suspicion of nitrofurantoin related pulmonary toxicity and cessation of the drug, I believe his management of [Mr A] over this period was consistent with accepted practice. Of note, [Mr A] had yet to develop significant shortness of breath and the normal chest X-ray findings were reassuring. [Dr C] was conscientious in seeking respiratory registrar advice on 22 [Month5] although it is not clear the registrar was informed of [Mr A's] prolonged use of nitrofurantoin. Had he received such information, I would expect the registrar to have recognised the possibility of drug induced pulmonary toxicity.

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9. On 9 [Month7] (18 days after the previous consultation) [Mr A] presented to [the medical centre]. Notes include: *1.5 weeks of progressively worsening SOB with pleuritic chest pain, cough productive in the mornings, no fevers, no haemoptysis …* [Mr A] was noted to be hypoxic (O_2 sats 76%) with borderline tachypnoea and tachycardia, and reduced air entry at both lung bases. He was referred acutely to [hospital] after administration of supplemental oxygen.

Comment: Management was consistent with accepted practice.

10. [C]hest imaging revealed changes consistent with acute pneumonitis attributed to likely nitrofurantoin toxicity and the drug was stopped. Despite aggressive management, [Mr A] developed respiratory failure and required prolonged ventilation in ICU. Sequential imaging showed progressive lung fibrosis as a result of the pneumonitis and [Mr A's] ventilatory requirements increased. On 19 [Month7] it was discussed with [Mr A] and his family that it was unlikely he could be weaned from the ventilator and his lung function was likely to deteriorate further. A palliative approach was agreed and [Mr A] was transferred to Hospice where ventilation was withdrawn and he died peacefully with family in attendance about an hour and a half later.

11. This has been a tragic case and the various providers involved have implemented remedial actions to reduce the risk of a recurrence:

(i) [The DHB] is to notify the GPs of the 1200 patients with spinal cord injury in the [spinal unit's] catchment area to highlight the side effects of nitrofurantoin and advising cessation of the antibiotic and review in patients who have been using it for over six months continuously. [Mr A's] case (anonymised) has been presented at the Mortality & Morbidity meeting.

(ii) [The pharmacy] have undertaken staff education and notified the Pharmacy Defence Association to ensure potential risks of long-term nitrofurantoin therapy is disseminated to all community pharmacists.

(iii) [The medical centre] has undertaken clinical education on the risks and monitoring requirements associated with long-term use of nitrofurantoin and a practice audit has been undertaken to ensure compliance with recommended monitoring requirements.

(iv) [Dr C] has personally undertaken further education and research in relation to nitrofurantoin-related pulmonary toxicity. He now uses the NZ Formulary as a resource for patient information leaflets he can use when prescribing medication.

(v) On the basis of the responses, it seems possible the relatively rare side effect of nitrofurantoin-related pulmonary toxicity is not well-recognised in primary care. This is despite information being provided by Medsafe and BPAC on several occasions over at least the past 18 years, and precautions featuring in relevant local HealthPathways. This might relate in part to the limited occasions on which a GP might consider prescribing long-term prophylactic nitrofurantoin, the rarity of the adverse effect, the multiplicity of sources GPs use to remain updated on clinical issues and the time required to remain abreast of all

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relevant clinical issues and updates. I recommend RNZCGP and HQSC be given the opportunity to consider how awareness of the medication risks in question can be further highlighted. There may be some value in RNZCGP recommending to members a clinical audit of nitrofurantoin use to ensure those patients on long-term prophylaxis are adequately informed and are being monitored and managed in accordance with national (HealthPathways) recommendations.

12. Extracts from the Medsafe datasheet on nitrofurantoin[14]:

- *Chronic pulmonary reactions (diffuse interstitial pneumonitis or pulmonary fibrosis, or both) can develop insidiously. These reactions occur rarely and generally in patients receiving therapy for six months or longer. Close monitoring of the pulmonary condition of patients receiving long-term therapy is warranted and requires that the benefits of therapy be weighed against potential risks.*
- *Hepatic reactions, including hepatitis, cholestatic jaundice, chronic active hepatitis, and hepatic necrosis, occur rarely. Fatalities have been reported. The onset of chronic active hepatitis may be insidious, and patients should be monitored periodically for changes in liver function.*
- *Chronic pulmonary reactions generally occur in patients who have received continuous treatment for six months or longer. Malaise, dyspnoea on exertion, cough, and altered pulmonary function are common manifestations which can occur insidiously. Radiologic and histologic findings of diffuse interstitial pneumonitis or fibrosis, or both, are also common manifestations of the chronic pulmonary reaction. Fever is rarely prominent.*
- *The severity of chronic pulmonary reactions and their degree of resolution appear to be related to the duration of therapy after the first clinical signs appear. Pulmonary function may be impaired permanently, even after cessation of therapy. The risk is greater when chronic pulmonary reactions are not recognised early.*
- *Acute pulmonary reactions are commonly manifested by fever, chills, cough, chest pain, dyspnoea, pulmonary infiltration with consolidation or pleural effusion on x-ray, and eosinophilia. Acute reactions usually occur within the first week of treatment and are reversible with cessation of therapy. Resolution often is dramatic.*

13. The Medical Council of New Zealand statement 'Good prescribing practice' (2010 version cited below, revised March 2020[15] but substantially unchanged) includes:

- *Be familiar with the indications, adverse effects, contraindications, major drug interactions, appropriate dosages, monitoring requirements, effectiveness and cost-effectiveness of the medicines that you prescribe.*
- *Ensure that the patient (or other lawful authority) is fully informed and consents to the proposed treatment and that he or she receives appropriate information, in a*

[14] https://www.medsafe.govt.nz/profs/Datasheet/n/nifurantab.pdf Accessed 12 November 2020
[15] https://www.mcnz.org.nz/assets/standards/ceae513c85/Statement-on-good-prescribing-practice.pdf Accessed 12 November 2020

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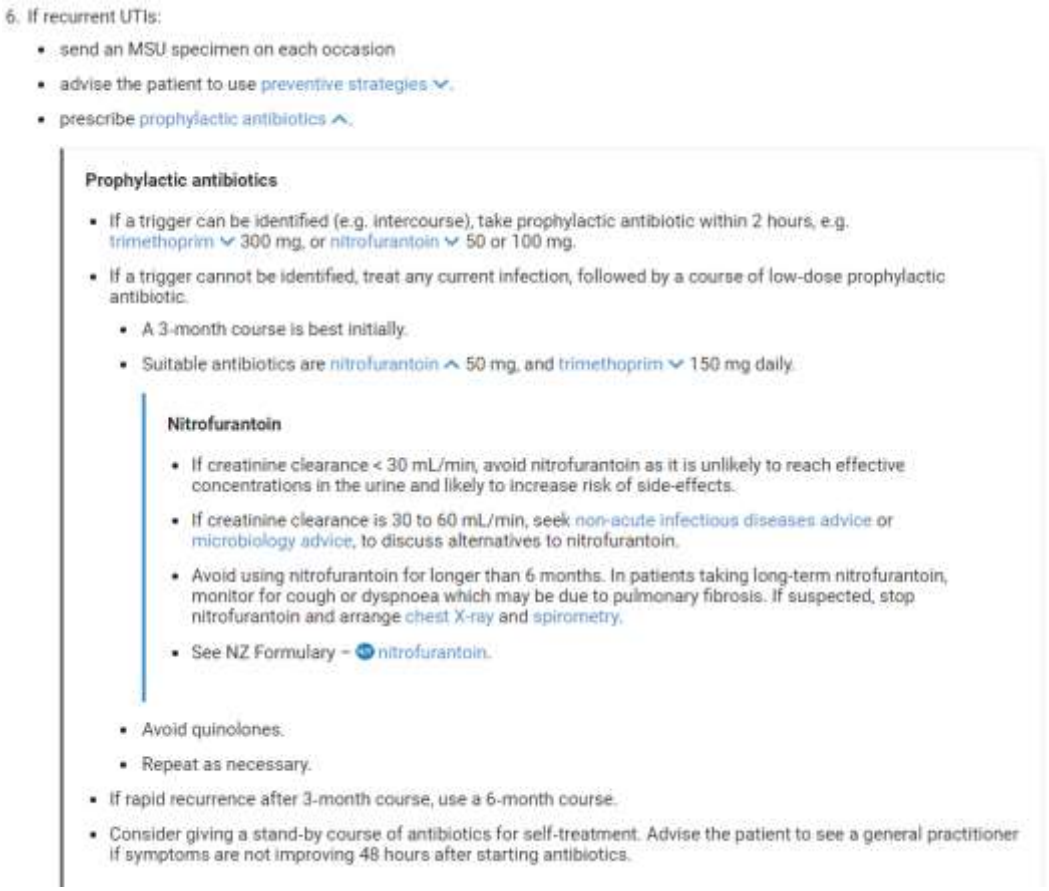
way they can understand, about the options available; including an assessment of the expected risks, adverse effects, benefits and costs of each option.

- *Periodically review the effect (benefits and harms) of the treatment and any new information about the patient's condition and health if the treatment is being prescribed for an extended period of time. Continuation or modification of treatment should depend on your evaluation of progress towards the objectives outlined in a treatment plan.*
- *Where a patient's care is shared between clinicians, the doctor with the responsibility for continuing management of the patient has a duty to keep him or herself informed about the medicines that are prescribed and the monitoring required for patients on that medicine to ensure safe and effective*
- *If you are the doctor signing and issuing the prescription you bear responsibility for that treatment; it is therefore important that, as the prescriber, you understand the patient's condition as well as the treatment prescribed and can monitor any adverse effects of the medicine should they occur.*

14. Local HealthPathways [16] includes the following advice currently (I am unable to determine if this advice has altered in recent years):



6. If recurrent UTIs:
   - send an MSU specimen on each occasion
   - advise the patient to use preventive strategies
   - prescribe prophylactic antibiotics

Prophylactic antibiotics

- If a trigger can be identified (e.g. intercourse), take prophylactic antibiotic within 2 hours, e.g. trimethoprim 300 mg, or nitrofurantoin 50 or 100 mg.
- If a trigger cannot be identified, treat any current infection, followed by a course of low-dose prophylactic antibiotic.
  - A 3-month course is best initially.
  - Suitable antibiotics are nitrofurantoin 50 mg, and trimethoprim 150 mg daily.

Nitrofurantoin

- If creatinine clearance < 30 mL/min, avoid nitrofurantoin as it is unlikely to reach effective concentrations in the urine and likely to increase risk of side-effects.
- If creatinine clearance is 30 to 60 mL/min, seek non-acute infectious diseases advice or microbiology advice, to discuss alternatives to nitrofurantoin.
- Avoid using nitrofurantoin for longer than 6 months. In patients taking long-term nitrofurantoin, monitor for cough or dyspnoea which may be due to pulmonary fibrosis. If suspected, stop nitrofurantoin and arrange chest X-ray and spirometry.
- See NZ Formulary – nitrofurantoin.

  - Avoid quinolones.
  - Repeat as necessary.
- If rapid recurrence after 3-month course, use a 6-month course.
- Consider giving a stand-by course of antibiotics for self-treatment. Advise the patient to see a general practitioner if symptoms are not improving 48 hours after starting antibiotics.

[16] Community HealthPathways. Section titled: Lower UTI in Men. Accessed 12 November 2020

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15. MPS has published case reports on complaints associated with complications of prolonged nitrofurantoin use. Learning points noted in a 2017 article[17] include:

- *Medical Protection sees a number of claims regarding inadequate monitoring of long-term nitrofurantoin with patients developing hepatic or pulmonary complications. Many claims relate to inadequate practice systems for monitoring.*
- *Expert opinion sought on these claims advises that BNF guidance for monitoring should be followed. The Medsafe datasheet gives similar advice as the BNF and can be viewed at: medsafe.govt.nz/profs/Datasheet/n/Nifurantab.pdf*
- *To screen for hepatic complications, repeat prescribing of nitrofurantoin should generate liver function tests (LFTs), at least six-monthly.*
- *To screen for pulmonary complications such as pulmonary fibrosis, doctors should advise patients starting on nitrofurantoin to attend urgently if they develop breathing problems. They could be reviewed for respiratory symptoms at the points of taking LFTs at least six-monthly, with consideration of more frequent monitoring.*'

Dr Maplesden also provided the following further advice:

> 'I have reviewed the responses to my original advice from [Dr C] and [the medical centre].
>
> Point 1) of [Dr C's] response (point 4 of my advice): [Dr C] states the decision on 23 April 2018 to extend the course of nitrofurantoin to six months was made with [Mr A's] consent following discussion of relief from repeated infections the initial course had provided him. Such discussion should include the potential risks versus benefits of extending the course. However, noting [Dr C] was apparently not aware of the risk of pulmonary toxicity associated with longer courses or repeated courses of the drug, it does not appear such discussion could have taken place. Given the relative rarity of pulmonary adverse effects and the relief [Mr A] had obtained from his treatment, he may well have decided the benefit of continuing treatment outweighed potential risk even had risks been presented, but this must be regarded as conjecture. The issue now is rather than criticism for extending the course of nitrofurantoin when there was apparently no robust clinical indication to do so, there could be criticism for the failure by [Dr C] to present the potential risk of pulmonary toxicity as part of the discussion. I believe this criticism has already been applied in other areas of my original advice so addressing purely the issue of whether or not continuation of nitrofurantoin was warranted from a clinical perspective, which was the basis for the adverse comment in my original advice, I withdraw that comment noting the decision was made jointly with [Mr A].
>
> Point 2): No change in my advice. I agree GPs cannot be expected to be familiar with every rare side effect of every drug prescribed. However, in the case of pulmonary toxicity of nitrofurantoin (a commonly prescribed drug), and the potential for this

[17] Fox A. Complications of Nitrofurantoin. MPS Casebook (NZ). 2017;25(2):16

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adverse effect to be fatal if not recognised early, Medsafe had recognised over many years that prescriber education was required in this regard and had undertaken such education on a number of occasions as had other agencies such as BPAC and more recently HealthPathways with the warning also present in manufacturer prescriber information, MIMS and New Zealand Formulary. I have acknowledged in my advice the difficulty of keeping abreast of such education and warnings but this does not obviate our need to do so.

Point 3). Has been addressed in existing advice and allowances made, when discussing the management of [Mr A's] pulmonary symptoms, for this gap in [Dr C's] knowledge.

Point 5. Remedial measures undertaken are appropriate.

I acknowledge [Dr C's] comment regarding possible lack of knowledge of the serious potential adverse effects of extended use of nitrofurantoin amongst his (and my) colleagues, hence the discussion in my original advice (s 11(v)) regarding possible involvement of RNZCGP and HQSC in determining how to most effectively disperse such information in the interests of patient safety.

[Medical centre's] response: I would regard the prescribing resources available to partners and employees as being consistent with accepted practice. The actions taken on receipt of the complaint are commendable — in particular liaison with the pharmacist to audit all patients prescribed nitrofurantoin and ensure adequate patient information has been provided and monitoring is in place where indicated. The practice Medications Reconciliation Policy and Repeat Prescribing Policy are fit for purpose and similar to those I have reviewed from other practices.'

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Appendix B: Independent clinical advice from Dr Andre Westenberg (urologist)

'Thank you for asking me to provide an opinion to the Commissioner on the care provided to [Mr A], case number **20 HDC 1462** by [Dr D], urology registrar.

I have read and agree to follow the Commissioner's guidelines for independent advisers.

I received my MBChB from Otago University in 1992. I was awarded my fellowship in Urology from the Royal Australasian College of Surgeons in 2000. I am a member of the Urological Society of Australia and New Zealand. As a general urologist I am well acquainted with the type of case under discussion. I am not aware of any actual or potential conflicts of interest.

I have been asked to comment on the following:

1. The reasonableness of the investigations undertaken by [Dr D] on 21 March 2018.
2. The adequacy of any advice and recommended monitoring provided to [Mr A's] GP by [Dr D] following the appointment on 21 March 2018. Please specifically comment on the reasonableness of [Dr D's] advice that [Mr A] continue taking prophylactic nitrofurantoin.
3. Any other matter that you consider warrants comment

For each of the above questions, I have been asked to advise on:

a. What is the standard of care/accepted practice

b. If there has been a departure from the standard of care or accepted practice, and how significant a departure you consider this to be

c. How would it be viewed by your peers?

d. Recommendations for improvement that may help to prevent similar occurrence in future.

My opinion is based on the documents sent to me by the office of the Commissioner which include:

1. A letter of complaint from [Mrs A] dated 11 August 2020,
2. [Second] District Health Board's response dated 29 September 2021,
3. A letter from [Dr D] dated 21 March 2018
4. [Spinal unit] notes and M and M discussion

Clinical summary:

[Mr A] had a history of traumatic T6 paraplegia with subsequent thoracic syrinx and consequent urinary retention. He suffered his traumatic paraplegia [many] years ago and was fit and healthy … He managed his bladder by means of self catheterisation.

He was seen by [Dr B] on 5 July 2017 where he was noted to have recurrent urinary infections for which he had been prescribed intermittent courses of ciprofloxacin. It was

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noted that his current KUB x-ray and ultrasound scan were unremarkable. He was prescribed nitrofurantoin 50 mg to take at night for 2 months. He was advised that if, after this period of prophylactic treatment, urinary infections persisted, he should be referred for urodynamic studies.

There is a letter from [the] general manager of the rehabilitation service at [the spinal unit] in September 2020 that states that [Dr B] advised that it is his routine practice to advise patients that nitrofurantoin could cause gastric irritation and that prolonged use of the medication can cause serious lung fibrosis. There is no documentation however that [Mr A] was advised of any of these potential side effects of nitrofurantoin when he was prescribed it in July 2017.

[Mr A] presented with further urinary infections ("12 urinary infections over the last 24 months, 9 over the past 12 months") and was seen by his GP, [Dr C]. I am not 100% clear from the provided notes but it appears that [Dr C] extended the original 2 months prescription for nitrofurantoin and referred [Mr A] to the urology clinic on 22 December 2017.

It was recommended that [Mr A] have an ultrasound and flexible cystoscopy to rule out renal or bladder stones as a nidus for infection. The referral was triaged to be seen within 4 months.

[Mr A] was seen at the urology clinic by [Dr D] in March 2018. It was noted that he had had only one urinary infection over the last 4 months and this was attributed to starting the nitrofurantoin. An ultrasound scan (report not provided), and a flexible cystoscopy were essentially normal. A recommendation was made that he continue with prophylactic nitrofurantoin as well as starting d-mannose. Regular follow up was to be continued in … private rooms.

There is no evidence of any discussion of the risks or side effects of any medications. There was no mention of any safety netting advice.

[Mr A] was referred acutely on 9 [Month7] to the respiratory team and was diagnosed with nitrofurantoin induced pneumonitis. Unfortunately this condition progressed and he passed away shortly after.

From [Mrs A's] letter of complaint it appears that between the time that [Mr A] was first prescribed nitrofurantoin in July 2017, and his eventual demise, there was only a 3-month period where he was not taking this medication.

After about 6–8 months on nitrofurantoin [Mr A] developed a dry cough but he was unaware that this could be a sign of underlying pulmonary disease secondary to nitrofurantoin. Despite a number of visits to the GP the connection between his symptoms and nitrofurantoin were not made until he presented to the emergency department in [Month7]. [Mrs A] alleges that neither [Dr B], [Dr C] or [Dr D], all who prescribed nitrofurantoin, gave

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any warnings about possible side effects and the implications of long-term use. In addition [the pharmacy] dispensing the medication also did not provide any information or warnings about potential side effects.

Nitrofurantoin is a useful antibiotic for urinary organisms. It has an unusual mode of action compared to other antibiotics in that its metabolites act on a number of different targets within bacteria. Due to its broad based mode of action bacterial resistance to nitrofurantoin is rare. It is useful against a number of urinary pathogens including enterococcus, staphylococcus, streptococcus, E. coli and Klebsiella. It is not useful for Proteus, Serratia or pseudomonas.

From the Med Safe data sheet nitrofurantoin is indicated as both a treatment and as prophylaxis for urinary infections. It should not be used in the presence of significant renal dysfunction nor in pregnant women.

There are a number of rare but important complications and these include the risk of pulmonary fibrosis, hepatic reactions and peripheral neuropathy. Pulmonary fibrosis may develop insidiously and it is recommended that close monitoring of the pulmonary condition of patients receiving long-term therapy is warranted and requires that the benefits of therapy be weighed against potential risks. Chronic pulmonary reactions generally occur in patients who have received continuous treatment for 6 months or longer and manifest as shortness of breath and cough. The severity of pulmonary fibrosis and the degree of resolution are related to the duration of therapy after the first clinical signs appear and pulmonary function may be impaired permanently even after cessation of therapy. The risk is greater when pulmonary reactions are not recognised early. It does not appear that pulmonary reactions are a dose related phenomenon.

A MedSafe prescriber update publication from June 2012 stressed that long-term use of nitrofurantoin (greater than 6 months), is associated with pulmonary toxicity. A further prescriber update publication on 5 March 2020 highlighted the risks of both hepatic and pulmonary toxicity with prolonged nitrofurantoin use. It is recommended that prophylactic therapy should not exceed 6 months unless the benefits clearly outweigh the risks and it is recommended that if therapy is continued beyond 6 months then monitoring should be in place with the patient encouraged to report the development of persistent cough or shortness of breath. Over the 10 years from 2009–2019 there were 46 reports of interstitial lung disease with 2 fatalities.

Opinion with regard to the specific questions asked by the Commissioner

1. The reasonableness of the investigations undertaken by [Dr D] on 21 March 2018.

[Mr A] presented with recurrent urinary infections. He managed his bladder by intermittent self catheterisation which is a risk factor for introducing infections but it is important to rule out causes of bacterial persistence such as renal or bladder stones and upper tract imaging with flexible cystoscopy were very reasonable investigations to undertake in this case and would be consistent with a good standard of care.

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2. The adequacy of any advice and recommended monitoring provided to [Mr A's] GP by [Dr D] following the appointment on 21 March 2018. Please specifically comment on the reasonableness of [Dr D's] advice that [Mr A] continue taking prophylactic nitrofurantoin.

From the notes it appears that [Mr A] had been plagued with recurrent urinary infections, "12 infections over the last 24 months". He had been assessed by the spinal team and had been given a two-month prophylactic course of nitrofurantoin. This appears to have been successful in controlling the urinary infections. I have not been provided with the GP notes and remain unclear whether the GP continued this course but it appears that he did. By the time [Mr A] was seen at the urology clinic in March 2018 therefore, he had already been on nitrofurantoin for over 6 months. When seen, it was noted that there had only been one urinary infection over the last 4 months. It was assumed (probably correctly), that this was a result of prophylactic nitrofurantoin and it was recommended that the course of prophylactic nitrofurantoin be continued.

There was no note of any discussion as to the risks and benefits of this course of action. There is no comment about the risks of a long course of nitrofurantoin. There is no note of any advice given regarding the importance and implications of the development of pulmonary symptoms whilst on nitrofurantoin.

Nitrofurantoin is an important medication in the arsenal of antibiotics used for the treatment of urinary infections. It is commonly used in community practice in a treatment dose as it is generally well tolerated and its mode of action means bacterial resistance is rare. It is less commonly used as prophylaxis but this is a safe and often effective strategy as long as the course is kept to less than 3 months. As outlined in the MedSafe prescriber updates quoted above, a treatment course longer than 6 months does increase the risk of the development of pulmonary fibrosis. Whilst this outcome is rare, it can be devastating and there is a strong recommendation that if it is considered that a prolonged course of nitrofurantoin is desirable, the risks and benefits are explained and that safety netting by means of a clear explanation of the requirement for monitoring of respiratory symptoms is necessary.

It does not seem there was any discussion about the benefits versus the risk of a prolonged course of nitrofurantoin was had with [Mr A]. There is no record of any advice regarding pulmonary monitoring.

Personally, I would have not continued prophylactic nitrofurantoin, its use had clearly "broken the cycle" of recurrent infections and causes of bacterial persistence had been ruled out. I think it would have been prudent to adopt a wait and see approach. There will be different schools of thought about this however and some clinicians would advocate for a prolonged course of prophylaxis.

If advocating this approach however, the risks of both pulmonary and hepatic toxicity ought to have been discussed and clear instructions regarding monitoring of pulmonary function

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in particular and the implications of the development of shortness of breath and a cough should have been explained to the patient and noted in the letter to the GP.

Unfortunately it does not appear that any of these risks were discussed and neither were the implications of the development of pulmonary symptoms. As such the opportunity for reversal of pulmonary fibrosis was missed and ultimately led directly to [Mr A's] demise.

The MedSafe data sheet and subsequent prescriber updates is very clear regarding the risks of long-term nitrofurantoin use. In my view the apparent failure to provide any discussion of the risks versus benefits of this prolonged course of antibiotics and the lack of any safety netting represents a significant departure from the standard of care.

Recommendations for improvement that may help to prevent a similar occurrence in future

The risk of nitrofurantoin toxicity with prolonged courses has been highlighted in at least 2 prescriber updates published by MedSafe over the last decade. I believe a more direct approach to the urology community by means of publication of the risks of long-term nitrofurantoin in the regular Uro News updates would be worthwhile. In addition the MPS case book is widely read by a range of medical practitioners and an anonymized article highlighting this particular case would provide good penetration.

Further comments following receipt of letters from [the pharmacy] and [Mr A's] GP received in August 2023

Thank you for providing me with this further information.

There is a letter from the pharmacist regarding the prescribing of nitrofurantoin and the local pharmacists' understanding of the risks of long-term use of this medication. Interestingly, not all the pharmacists were aware of the risk of pulmonary fibrosis with the long-term use of this medication. In addition, and I think probably appropriately, comment was made that very rare side effects of medication are not routinely discussed. The medicine information sheet supplied (published by medinfo.co.nz) only mentions "lung problem" *(sic)* in passing, and certainly does not highlight the very rare but significant side effect of pulmonary fibrosis. I agree with the pharmacist's point that prescription of this medication is a clinical decision made by the prescribing doctor.

Looking at the medications prescribed (and presuming all prescribed tablets were taken), 60 tablets of low-dose (50 mg) nitrofurantoin was initially prescribed by the spinal outreach clinic in July 2017. This was a once-a-day (prophylactic) dose. In November [Dr C], his GP, prescribed a further 111 tablets; a treatment dose for 7 days (4 tablets/day) and then the remainder were to be taken as prophylaxis at one tablet per day, giving a total of 90 days of treatment. Presuming that these tablets were all taken as prescribed, and that none of them were lost, these would last until 6 February 2018. A treatment dose of 28 tablets (4 tablets/day) were prescribed in December 2017 with 2 28 tablet treatment dose repeats which were dispensed at the end of December, January and March. Two further treatment

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courses of 28 tablets were prescribed in March 2018. [Mr A] was referred to the urology department in December 2017.

He was seen in March 2018 and had an ultrasound and flexible cystoscopy to rule out bacterial persistence and, given the apparent good response to the previously instituted low-dose nitrofurantoin prophylactic regimen, a further 90 tablet prophylactic course was instituted and dispensed on 28 April 2018. A further 90 tablets were given in August 2018 and then another 90 tablets in October 2018. At this point, apparently [Mr A] had not had a urinary infection for over 12 months and at the end of this course which would have been around December 2018 the nitrofurantoin was discontinued. He unfortunately developed another urinary infection and prophylaxis was resumed with a further 111 tablets dispensed at the end of [Month2] (presumably this is a 7 day treatment course and then 11 week prophylaxis of 1 tablet/day). Another 3 months course of treatment, 90 tablets, were prescribed in [Month4].

Assuming my maths is correct, nearly 800 (782) 50 mg nitrofurantoin tablets were dispensed over the course of just over 12 months. Over an approximately 28 month period from July 2017 there appear to have been only 2 breaks in treatment, from mid September 2017 to early November 2017 and from [early] 2019 to [Month2]. There was a 15-month period of essentially continuous use of nitrofurantoin between November 2017 and [early] 2019.

[Dr C] has also written a report on this case. He was obviously devastated by the outcome. He states that he was unaware of the potential pulmonary toxicity with long-term nitrofurantoin use and that his colleagues were also unaware of this risk. As mentioned above only some of the pharmacists were aware of this risk.

You had asked me to specifically comment on the care provided by [Dr D], urology registrar. In my previous report (included above) I had considered that the ongoing use of prophylactic nitrofurantoin in the absence of any specific safety netting with regard to warning [Mr A] about the potential for pulmonary toxicity represented a significant departure from the standard of care. I would like to revise this opinion.

Personally I am very aware of the association between long-term nitrofurantoin and pulmonary toxicity as I have been involved with a patient who has suffered this complication. Nitrofurantoin is widely used as prophylaxis against urinary infections. The complication of pulmonary fibrosis is rare and if one had never come across anyone who had suffered it, it would not be at the front of one's mind. Both the pharmacist involved in this case and the GP, [Dr C], were not aware of the association, and neither were most of their colleagues. It appears that [Dr D] was also unaware of the association. [Dr B] of the spinal outreach clinic clearly was aware and reports that it is his practice to warn patients of the risk of pulmonary toxicity but this is not documented and [Mrs A] does not recollect this warning.

[Mr A] had a long course of continuous low-dose nitrofurantoin and suffered the rare complication of pulmonary fibrosis which unfortunately led to his demise. Most patients taking nitrofurantoin do not suffer this complication. It appeared that nitrofurantoin was having a positive effect on the incidence of urinary infections and the medication was

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therefore appropriately prescribed. The medication was prescribed by a number of clinicians. Neither [Dr B], [Dr C], [Dr D] nor the pharmacist warned [Mr A] about the very rare risk of pulmonary fibrosis. Given the above, although the outcome has been devastating I consider that the departure from the standard of care with regards to [Dr D's] input is relatively minor.

I hope the above is helpful. Please do not hesitate to contact me if you require any further information.

Kind regards

Yours sincerely

Andre Westenberg FRACS'

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Appendix C: Independent clinical advice from Ms Pauline McQuoid (pharmacist)

'Please review the enclosed prescriptions and labels of nitrofurantoin and advise whether you consider the care provided to [Mr A] by [the pharmacy] was reasonable in the circumstances, and why.

Please discuss:

1. The pharmacist and pharmacy's obligations to [Mr A] in these circumstances

In addition to the legal obligations on pharmacists, which includes the obligations in the Health and Disability Code of Rights, there are ethical, professional and contractual obligations on pharmacists. Aspects of these that are relevant to the case are described below.

There is remarkably little information on a pharmacist's specific obligations regarding advising patients on serious but rare side effects of medicines. In pharmacy practice, this is commonly referred to as "patient counselling".

Ethical:

The Pharmacy Council of NZ (PCNZ) Code of Ethics 2018 articulates "the professional and ethical values to which all pharmacists should conform and can expect of their colleagues."

It states that:

> "A pharmacist is professionally accountable for their practice, which means being responsible for their actions or inaction, no matter what advice or direction a manager or another professional gives them."

Professional

i) PCNZ Competence standards for [the pharmacy] profession 2015

   Standard O3 — Supply and administration of medicines

   "Patient counselling requires you to take into account not only your expertise to provide medication information, but also to consider the patient as an expert in their life. You have a duty of care to the patient to ensure the prescriber's intentions are clear, and the patient understands and is able to use the medicine(s) safely and effectively."

   O3.5 PROVIDE PATIENT COUNSELLING

   O3.5.3 Provides the patient with sufficient information to ensure the safe and proper use of medicine(s), including effective use of devices

ii) PSNZ Guide for Pharmacist salary banding in NZ 2017 describes expectations of pharmacists in different roles. Patient counselling is included as one of the "dispensing pharmacist" functions.

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"Providing information, education and advice on prescription medicines designed to maximise health outcomes and patient understanding. This should occur for all newly prescribed medicines when first dispensed, and checked for adherence and adverse events on repeat dispensing. It is the provision of technical instructions (medicine name, strength, dose, frequency) and information (common adverse effects, standard precautions) to ensure safe and optimal use of medicines."

iii) Pharmaceutical Society of NZ Pharmacy Practice Handbook 2021

This is a practical guide for pharmacists, providing "advice for the professional delivery of pharmacist services to achieve good pharmacy practice." It offers the following guidance on the expectations of pharmacists regarding patient counselling:

Pharmacists play an important role in the delivery of healthcare to the community and may often be the first, only or last point of contact with the patient. They are responsible for ensuring that the patient understands how to use their medicines safely and effectively.

Our effectiveness as pharmacists depends both on the quality of the information given to the patient and on the quality of the communication with the patient. The information given to the patient should give a balanced view of the potential therapeutic benefits and risks.

It is not sufficient to dispense and supply a medicine with only written information, the advice needs to be tailored to the individual as pre-printed leaflets may be outdated, unvalued and ineffective.

The pharmacist should also be looking beyond just filling the prescription and should be considering the patient's health holistically. The pharmacist should be reviewing the suitability of the medicine in the context of the patient and their regular/usual medicines and considering if the dose seems appropriate or if the medicine will interact with another medicine, and considering any advice that should be given with the medicine for the person to achieve optimal use and therapeutic effect. Any concerns should be addressed with the prescriber.

Before leaving the pharmacy the patient should understand:

- Why the medicine has been prescribed
- How to take it
- When to take it
- For how long to take it
- How to recognise side effects and what to do if side effects occur
- What special precautions to take, foods or medicines to avoid
- Correct storage of the medicine
- If there are repeats or a balance owing how and when to collect them
- What to do if they think the medicine is not working
- When to contact the doctor and the appropriate disposal of any unused medicine.

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Ideally, the patient should have knowledge of the following:

- Name and description of the medicine
- Intended purpose and expected action
- Route of administration, dosage, dosage form and administration schedule
- Any special directions or precautions to be taken
- Common side-effects that may be encountered, ways in which to minimise them and action required if they occur
- Details of discontinued medicines and their relationship to new medicines
- Appropriate storage requirements
- Length of therapy and source of further supplies
- Action to be taken in the event of a missed dose
- Lifestyle / self-care advice
- The importance of a follow-up consultation and when this should occur – as directed by good pharmacy practice
- When the patient should seek medical advice and where to go for advice if symptoms don't improve within recommended time frame:
    - The availability of the pharmacist for further information if required
    - Dr - own GP or after-hours service
    - Hospital - emergency department.

Contractual

All pharmacies have a contract with their DHB — the Integrated Community Pharmacy Services Agreement (ICPSA). It states the following regarding professional services:

SCHEDULE 1

DISPENSING AND PROFESSIONAL ADVISORY SERVICES

Professional Advisory Services requirements

The Provider must provide the following Professional Advisory Services:

(a) in relation to any Pharmaceutical it Dispenses to or for a Service User in accordance with clause **Error! Reference source not found.** of this Schedule, u ndertake a check in accordance with legal and professional requirements, including to ensure that:

(i) the Pharmaceutical specified in the Prescription Form is clinically appropriate for use by the Service User; and

(ii) the Prescription Form:

(1) meets all legal and professional requirements; and

(2) meets the criteria for payment set out in the Pharmaceutical Schedule; and

(b) provide, in accordance with professional standards and any relevant guidelines, professional advice and counselling to the Service User, as and when is clinically appropriate, to ensure that the Service User has sufficient knowledge to enable optimal therapy.

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Advise on whether [the pharmacy] and pharmacists' management, knowledge of and communication about nitrofurantoin was adequate from 2017 to 2019.

Please advise:

a) What is the standard of care/accepted practice?

There are two main issues. Firstly, whether the patient counselling was adequate, and secondly, whether the pharmacist should have picked up that the medicine was being prescribed for longer than recommended.

i) Patient counselling:

As outlined above, pharmacists are expected to provide advice to patients when they dispense medicines and this advice should include information on adverse effects. However, there is no specific guidance relating to whether or how much information should be provided on rare but serious adverse effects, such as the lung damage that [Mr A] experienced. Every medicine has a very long list of adverse effects listed in the official information and it is always difficult to know how much of this to convey to the patient to achieve a balance of information without causing unnecessary alarm, given that the majority of people will experience few, if any, adverse effects. We also know that people retain less than 30% of the information that health professionals impart, so an accepted approach is to provide information on the common adverse effects that people are more likely to experience initially, then build on that over time. Pharmacists will often provide written information to supplement the verbal information.

In my opinion and experience, it would not be unusual for a pharmacist to omit information about rare adverse effects with the initial dispensing, especially for a treatment (such as an antibiotic) that is intended for the short term.

In summary, the standard of care/accepted practice is that the pharmacist should have provided verbal information on the common adverse effects, preferably supplemented with written information. However, when the nitrofurantoin was prescribed as a regular medicine in April 2018, "good practice" is that the pharmacist should have followed up with information about longer-term adverse effects and symptoms for which to monitor (respiratory, neurological).

ii) Duration of therapy:

The first dispensing of nitrofurantoin was for 2 months of prophylactic treatment, i.e. once a day. A six week break followed, then a series of treatment courses where the antibiotic was given four times a day for usually seven days, followed by once a day prophylactic dosing. This continued for about four and a half months. It would not be considered unusual for a person who self-catheterises to have repeated courses of oral antibiotics. About 25% of patients who self-catheterise experience recurrent symptomatic UTIs. After this time [Mr A] was prescribed nitrofurantoin once a day for ten months continuously, then a break of 3 months, then once a day for another six months, after which time he developed the fatal lung damage. On one hand, principles of antimicrobial stewardship should prompt a

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pharmacist to question why a person is taking long-term antibiotics prophylactically. On the other hand, using nitrofurantoin for long-term UTI prophylaxis was not unheard of at that time. A paper published in the reputable medical journal The Lancet infectious diseases in 2018 reported that 12 months of low-dose prophylactic antibiotics (including nitrofurantoin) halved the incidence of UTIs in people who self-catheterise intermittently, suggesting that this was considered a reasonable therapeutic approach at that time. This is somewhat surprising, considering the warnings that had been issued about pulmonary damage associated with nitrofurantoin, including fatal pulmonary fibrosis. NZ Medsafe published information on this in the monthly Prescriber Update bulletin in 2002, 2012 and 2015, however pharmacists would not be expected to subscribe to Prescriber Update. Notwithstanding this, I would expect people prescribing or dispensing nitrofurantoin in 2017, 2018 and 2019 to be aware that giving nitrofurantoin for longer than six months increases the risk of serious pulmonary adverse effects and should be avoided. In April 2018 when the nitrofurantoin was prescribed as a regular long-term medicine (this was apparent because it was prescribed for three months rather than as short courses) I think the prescriber should have been contacted and alerted to the dangers of continuing nitrofurantoin for longer than six months. However, there would not be consensus about this across the profession and many community pharmacists would disagree.

b) If there has been a departure from the standard of care or accepted practice, how significant a departure (mild, moderate, or severe) do you consider this to be?

For omitting to inform the patient about the serious and rare adverse effects of nitrofurantoin and for omitting to alert the prescriber to the risks of using nitrofurantoin for long term prophylaxis, I believe these are not a departure from the accepted standard of practice for short-term use. For use beyond six months they are a mild to moderate (due to lack of consensus within the profession — some would consider it mild and others would consider it moderate) departure from standard practice.

How would it be viewed by your peers?

As stated above, I believe there would not be consensus across [the pharmacy] profession. It is likely that many community pharmacists would view it as an unfortunate but inevitable consequence of time and cost pressures in that sector (with which my peers and I disagree). Others (such as me and my peers) would consider it to be a moderate failure in care to have not recognised that the nitrofurantoin was being prescribed long-term from April 2018 after [Mr A] had already received about 7 months treatment, and to then advise him or whomever was collecting his medicines about the risks of long-term adverse effects (respiratory, neurological) and symptoms for which to monitor, and to have alerted the prescriber to the risks of continuing nitrofurantoin beyond six months.

c) Recommendations for improvement that may help to prevent a similar occurrence in future.

The most reliable way to avoid this happening again is to restrict the availability of nitrofurantoin for long-term use by restricting the Pharmac subsidy beyond six months' use to "special authority" approvals only, with specific criteria that must be met in order for the

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medicine to be subsidised. Whilst prescribers could still find ways around this system, it would be a way of alerting them to the risks of longer-term use.

Other mechanisms are computerised alerts on general practice systems and dispensing systems. Both of these have a low chance of success.

Prescriber and pharmacist education are always good to encourage but very unreliable to prevent this specific problem happening again. Every pharmacist and prescriber can't know every rare and serious adverse effect of every medicine, but we need to ensure that there are enough checks and balances in the system to make up for knowledge gaps. This would require a multifaceted approach.

…

Pauline McQuoid
MPharm, RegPharmNZ (Prescriber)'

Ms McQuoid also provided the following further advice:

> 'My apologies for not responding sooner. I have refamiliarised myself with the details of [Mr A's] case. I appreciate the considered response that [the pharmacist] has provided however it does not change my advice, as I have already acknowledged in my advice the lack of consensus within [the pharmacy] profession about where the professional responsibility lies, and lack of awareness about rare but serious adverse effects.
>
> [The pharmacist] raises good points in defence of their professional practice.
>
> 1. The pharmacy "had several patients who were on long-term Nitrofurantoin prophylaxis. It was not common, but certainly not unusual for us to see prescriptions for daily Nitrofurantoin".
>
> Even when we see something prescribed by others, we are still professionally responsible to confirm for ourselves that a prescribed medicine is appropriate, even when it is the continuation of a previously prescribed medicine. Just because someone else has done it doesn't mean it is OK.
>
> 2. "As a community pharmacist, you have to trust that the prescriber has made a conscious choice to start a patient on long-term Nitrofurantoin after assessing the risks and benefits, especially if they have been taking multiple short courses of it."
>
> I can understand this stance but as pharmacists we well know that prescribers don't know everything about medicines and part of our professional responsibility is to bring information to the prescriber's attention to ensure that the prescriber has all the information they need to prescribe safely. Pharmacists do this every day across NZ.
>
> In [Mr A's] case, one of the contributory factors was multiple prescribers. A urologist initiated the treatment and several different prescribers repeated it. Multiple

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prescribers and prescribing across care settings are two well-recognised risks for medication error.

"I would assume that by prescribing this medicine long term, monitoring a patient for pulmonary reactions and function would be part of this assessment by the prescriber. At a community pharmacy, I would not consider it to be the pharmacist's responsibility to notify the prescriber of the need for this. There are many medicines that require monitoring by the prescriber, and community pharmacists are not generally provided with evidence as to whether this monitoring is occurring. It would not be practical to check with the prescriber every time a patient is prescribed a medicine that requires monitoring, and I would not consider this to be part of the pharmacist's responsibility. I would expect the pharmacist to get in contact if they had any specific concerns. I would also expect this to be a part of the pharmacist's role when they were working within a medical centre or if they were conducting a higher-level review of the patient's medicines, such as a Medicine Therapy Assessment. Pulmonary reactions are rare and pharmacists in community pharmacy do not have access to enough information about the patient to be responsible for ensuring that the prescriber is monitoring their patient for a specific rare reaction to a medicine."

[The pharmacist] is absolutely correct that the prescriber should monitor the patient. My expectation was not that [the pharmacy] would have to monitor the patient, nor to tell the prescriber to monitor the patient. However, the prescriber might not know about the rare but serious and potentially fatal pulmonary toxicity associated with long-term nitrofurantoin. The expectation would be that the pharmacist contact the prescriber to highlight the risk of long-term prophylaxis with nitrofurantoin. Many pharmacists contact prescribers several times a day to point out issues with prescriptions, this is an accepted part of our practice.

As I stated in my original advice, we, health professionals working in the health system, will continue to kill more New Zealanders every year than suicide and road deaths combined (and doubled), unless medication harm is recognised and taken seriously, and treated as something we all have responsibility for rather than assuming that it's not our job and someone else is doing it.

Kind regards,

Pauline McQuoid
Clinical Pharmacist, Medwise'

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