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Spotlight on nitrofurantoin

Key messages

- Nitrofurantoin is indicated for the treatment or prophylaxis of urinary tract infection.
- Adequate renal function is needed to achieve an effective therapeutic concentration in the urine.
- Nitrofurantoin is contraindicated in patients with an eGFR less than 60 mL/minute/1.73 m² due to the increased risk of toxicity and decreased efficacy.
- The risk of pulmonary and hepatic adverse reactions increases with prolonged use.
- 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.

This article on nitrofurantoin continues the spotlight series where Medsafe reviews the safety information on a specific medicine. The Centre for Adverse Reactions Monitoring continues to receive serious adverse reactions reported in association with nitrofurantoin use.

Please refer to the medicine data sheet for full prescribing information:
medsafe.govt.nz/profs/Datasheet/n/Nifurantab.pdf

Indication

Nitrofurantoin is a bactericidal antibiotic with activity exclusively in the urine¹. It is indicated for the treatment and prophylaxis of urinary tract infections (UTIs) caused by susceptible bacteria².

Antimicrobial susceptibility data from New Zealand hospital and community laboratories indicate most urinary *E. coli* infections are susceptible to nitrofurantoin³. Nitrofurantoin is not effective against *Pseudomonas*, *Proteus* and *Serratia* species^{2,4}.

The recommended duration of treatment with nitrofurantoin for long-term prophylaxis against UTIs is up to 6 months. Only continue beyond 6 months when the benefits clearly outweigh the risks^{2,5} and monitoring is in place to detect signs of nitrofurantoin toxicity (described below).

Mechanism of action

Bacterial flavoproteins reduce nitrofurantoin to reactive intermediates in the acidic urinary environment. The reactive intermediates interfere with bacterial ribosomal proteins and other macromolecules, inhibiting several biochemical and synthetic processes in the bacterial cell^{1,2}. This multi-modal mechanism of action is believed to contribute to the relatively low level of acquired bacterial resistance to nitrofurantoin^{2,4}.

Use of nitrofurantoin in renal impairment

Adequate glomerular filtration and renal tubular secretion is needed to achieve an effective therapeutic concentration in the urine¹. In patients with normal renal function, therapeutic doses of nitrofurantoin are rapidly excreted into the urine with no build-up in the plasma. In patients with impaired renal function, the plasma concentration increases and there is a higher risk of nitrofurantoin toxicity².

Significant renal impairment (eg, eGFR less than 60 mL/minute/1.73 m²) is a contraindication to nitrofurantoin². The Medicines Adverse Reactions Committee recently reviewed the evidence for safe use of nitrofurantoin in patients with a greater degree of renal impairment but considered that the available evidence did not support lowering the eGFR cut-off point^{6,7}.

Adverse effects

Monitoring requirements

Monitor patients on long-term prophylaxis for changes in clinical status that may increase the risk of nitrofurantoin toxicity^{1,2}. Discontinue nitrofurantoin at the first sign of toxicity.

Pulmonary reactions

Pulmonary reactions to nitrofurantoin may occur with short-term or long-term use. The reactions do not appear to be dose-related⁸.

Acute interstitial pneumonitis is a type of hypersensitivity reaction that may occur within 1–2 weeks of starting nitrofurantoin. Typically, it presents with fever, dry cough, chest pain and dyspnoea, with eosinophilia and radiological evidence of pulmonary infiltration. Acute reactions to nitrofurantoin are reversible on stopping the medicine^{2,8}.

Chronic pulmonary reactions may develop after several months (usually more than 6 months) of low-dose nitrofurantoin and are thought to be either a cell-mediated or toxic response⁸. Chronic interstitial lung disease may develop insidiously, typically presenting with dyspnoea, dry cough and fatigue. Monitor lung function in patients on long-term nitrofurantoin and advise patients to report new or worsening symptoms of cough or shortness of breath. Discontinue nitrofurantoin at the first sign of pulmonary toxicity. The risk of permanently impaired lung function increases with delayed diagnosis².

Hepatic reactions

Nitrofurantoin can cause an autoimmune-like hepatitis with prolonged use^{9,10}. Monitor liver function periodically in patients on long-term prophylaxis with nitrofurantoin and stop the medicine immediately if hepatitis develops^{1,2}. Hepatitis associated with short-term use of nitrofurantoin has been reported but is very rare¹⁰.

Peripheral neuropathy

Nitrofurantoin toxicity causes peripheral neuropathy (including optic neuritis), which may be severe and irreversible. Renal impairment increases the risk of peripheral neuropathy due to reduced clearance of nitrofurantoin from the blood. Other risk factors include anaemia, diabetes mellitus, electrolyte imbalance, vitamin B deficiency and debilitating disease. Monitor patients on long-term prophylaxis periodically for changes in renal function that may increase the risk of nitrofurantoin toxicity². Inform patients on prophylactic nitrofurantoin about symptoms of peripheral neuropathy and examine them periodically for signs of nerve damage.

Haemolytic anaemia

Nitrofurantoin may cause haemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. If haemolysis occurs in these patients, discontinue treatment with nitrofurantoin.

There is also a risk of haemolytic anaemia in newborn infants with G6PD deficiency if exposed to nitrofurantoin *in utero* close to delivery or through breast milk. For this reason, nitrofurantoin should be avoided in late pregnancy and, if breastfeeding, for the first month after the birth².

Interactions

Antacids containing magnesium trisilicate (eg, Quick-Eze) reduce the absorption of nitrofurantoin, which may reduce its antibacterial effect in the urine².

New Zealand adverse reaction reports

During the 10-year period to the end of 2019, the Centre for Adverse Reactions Monitoring (CARM) received 150 adverse reaction reports in which nitrofurantoin was a suspect medicine. Most of the reported reactions occurred in female patients (133 reports), consistent with the higher use of nitrofurantoin for UTIs in women. Age at the time of the reaction ranged from 9 years to 94 years (median 67 years), consistent with higher use among older patients. Reports for interstitial lung disease, hepatic reactions and peripheral neuropathy are described below.

- Interstitial lung disease: 46 reports, of which 29 were serious, including two fatal reports.
- Hepatic reactions: 17 reports, including three reports of hepatic cirrhosis and one report in which the patient also had pneumonitis. Of these reports, 12 were assessed as serious, but none were fatal.
- Peripheral neuropathy: 3 reports.

References

1. New Zealand Formulary. 2020. *New Zealand Formulary v91: Nitrofurantoin* 1 January 2020. URL: nzf.org.nz/nzf_3293 (accessed 17 January 2020).
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9. Larson A. 2019. Drug-induced liver injury. In: *UpToDate* 10 May 2019. URL: uptodate.com/contents/drug-induced-liver-injury (accessed 17 January 2020).
10. LiverTox. 2014. *Nitrofurantoin* 7 February 2014. URL: ncbi.nlm.nih.gov/books/NBK548318/ (accessed 17 January 2020).

Isotretinoin: Why it's important to prevent pregnancy

Key messages

- Isotretinoin is contraindicated during pregnancy. It is highly teratogenic at all therapeutic doses, and congenital malformations have been reported following a single dose taken during pregnancy.
- When prescribing isotretinoin to women of childbearing potential, ensure adequate pregnancy prevention measures are in place, including at least two forms of effective contraception.
- A pregnancy test is recommended within three days prior to starting treatment, every month during treatment and five weeks after stopping treatment.
- Decision support tools are available to support appropriate prescribing of isotretinoin.
- Dispense isotretinoin in the manufacturer's original pack.

Isotretinoin indicated for treatment of severe acne

Isotretinoin is a synthetic vitamin A derivative (retinoid) indicated for the treatment of patients with severe forms of nodulocystic acne that persist following other treatments¹. Isotretinoin suppresses sebaceous gland activity leading to reduced sebum production, smaller sebaceous glands, less follicular occlusion and less inflammation².

Isotretinoin is teratogenic

Isotretinoin is teratogenic at all therapeutic doses. Fetal malformation may occur with only a short period of exposure to isotretinoin during pregnancy¹ and has been reported after a single dose³.

Isotretinoin embryopathy consists of craniofacial, cardiac, thymic and central nervous system malformations⁴. Isotretinoin adversely affects 25–40 percent of fetuses exposed during embryogenesis (ie, the first 10 weeks following conception)⁵. For pregnancies that end in birth, the rate of malformations associated with isotretinoin exposure in utero has been reported as 11–30 percent, with most estimates at the upper end of this range⁶. Fetal exposure to isotretinoin beyond the critical period of organogenesis can cause developmental delays and other central nervous system effects in approximately 40 percent of cases⁴.

Isotretinoin exposure is still occurring in pregnancy

Despite the well-known teratogenic effects of isotretinoin, pregnancy exposures still occur. A review of the National Collections data indicated that during the period 1 July 2011 to 30 June 2017, 39 live-born infants were potentially exposed to an oral retinoid during pregnancy or within 30 days of the estimated pregnancy start date. In 31 of these cases, isotretinoin was dispensed after the estimated pregnancy start date. This number is likely to be an underestimate as the data does not include pregnancies that ended prior to 20 weeks gestation⁷.

Isotretinoin is contraindicated in pregnancy

Acne commonly occurs in adolescents and young adults. Due to its teratogenic effects, isotretinoin is contraindicated in pregnancy. Extreme care is therefore required when prescribing isotretinoin to treat acne in women of childbearing age – only prescribe if the conditions in Table 1 are met.

Table 1: Conditions that must be met when prescribing isotretinoin to treat acne in a woman of childbearing potential^{a,b,c}

- Severe acne that is resistant to other therapies.
- Can understand the need for pregnancy prevention and is willing to adhere to the requirements.
- Has been informed by her doctor of the hazards of becoming pregnant during and 1 month after treatment with isotretinoin, she has been warned of the possibility of contraceptive failure and she confirms that she has understood the warnings.
- Is willing to use two forms of effective contraception (ie, a barrier method and hormonal contraception) without any interruption for 1 month before starting isotretinoin, during treatment with isotretinoin and for 1 month after stopping isotretinoin. Oral progesterone-only contraceptives are not considered an effective form of contraception during treatment with isotretinoin.
- Has a negative pregnancy test within 3 days prior to starting treatment with isotretinoin. Repeat pregnancy tests monthly and 5 weeks after stopping treatment.
- Starts isotretinoin therapy only on day 2 or 3 of the next menstrual period.

- a. Douglas Pharmaceuticals Ltd. 2019. *Oratane New Zealand Data Sheet* 29 October 2019. URL: medsafe.govt.nz/profs/Datasheet/o/oratanecap.pdf (accessed 10 January 2020).
- b. New Zealand Formulary. 2020. *New Zealand Formulary v91: Isotretinoin (systemic)* 1 January 2020. URL: nzf.org.nz/nzf_6452 (accessed 10 January 2020).
- c. BPAC NZ. 2017. *Prescribing isotretinoin for patients with acne in primary care* 20 January 2017. URL: bpac.org.nz/2017/isotretinoin.aspx (accessed 9 January 2020).

Contraceptive measures should be continued for one month after stopping isotretinoin to ensure that the drug and its active metabolite have completely cleared from the body¹.

Additional measures to reduce the risk of pregnancy exposure to isotretinoin

There are decision support tools available to support the appropriate prescribing of isotretinoin. The *bestpractice* isotretinoin module contains information about appropriate pregnancy prevention measures and contains a printable patient acknowledgement/consent form (bestpractice.net.nz/feat_mod_NatFunded.php#isotretinoin). Oratane is currently the only funded brand of isotretinoin available in New Zealand. Additional materials are available from Douglas Pharmaceuticals at: oratane.co.nz

Dispense isotretinoin in the manufacturer's original pack. The pack contains safety information, including information on pregnancy prevention⁸. A copy of the Consumer Medicine Information leaflet should also be given to the patient when isotretinoin is dispensed for the first time (available at medsafe.govt.nz/Medicines/infoSearch.asp).

Exposure to isotretinoin via semen is not believed to cause teratogenic effects. Advise male patients not to share their isotretinoin with anyone¹.

Patients taking isotretinoin should not donate blood during treatment and for at least one month after stopping the medicine^{1,2}.

References

1. Douglas Pharmaceuticals Ltd. 2019. *Oratane New Zealand Data Sheet* 29 October 2019. URL: medsafe.govt.nz/profs/Datasheet/o/oratanecap.pdf (accessed 10 January 2020).
2. New Zealand Formulary. 2020. *New Zealand Formulary v91: Isotretinoin (systemic)* 1 January 2020. URL: nzf.org.nz/nzf_6452 (accessed 10 January 2020).
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8. Medsafe. 2018. *Minutes of the 174th Medicines Adverse Reactions Committee meeting*. URL: medsafe.govt.nz/profs/adverse/Minutes174.htm#3.2.4 (accessed 10 January 2020).

Acitretin: Changes to pregnancy prevention requirements

Key messages

- Acitretin is contraindicated in women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met.
- The period during which effective contraception must be used has increased from two to **three** years after the end of treatment.

Acitretin is a teratogenic medicine used to treat several skin conditions, including psoriasis. It is contraindicated in women of childbearing potential unless they follow all of the conditions of the Pregnancy Prevention Programme¹. Recently, there has been a change to the requirements to take effective contraception following completion of treatment: women must now use effective contraception for **three years** (36 months). The change has occurred since the formation of etretinate in the presence of alcohol has been discovered. The half-life of etretinate is 120 days¹, resulting in the increased post-treatment contraception requirements.

Prescribers are asked to remind women of childbearing potential of the Pregnancy Prevention Programme requirements. In particular, any woman requiring treatment should understand that she must consistently and correctly use one highly effective method of contraception (ie, a user-independent form) or two complementary user-dependent forms of contraception, for at least one month prior to starting treatment, throughout the treatment period and for at least three years (36 months) after cessation of treatment. Oral progesterone-only contraceptives are not considered an effective form of contraception during treatment with acitretin².

Novatretin is the only approved acitretin product currently available in New Zealand. The pregnancy warning on the Novatretin package label and foils has been updated from 24 to 36 months (Figure 1).

Figure 1: Image of the Novatretin (acitretin) package foils



References

1. Douglas Pharmaceuticals Ltd. 2019. *Novatretin New Zealand Data Sheet* 8 October 2019. URL: medsafe.govt.nz/profs/Datasheet/n/novatretincap.pdf (accessed 17 December 2019).
2. New Zealand Formulary. 2020. *New Zealand Formulary v91: Acitretin* 1 January 2020. URL: nzf.org.nz/nzf_6379 (accessed 30 January 2020).

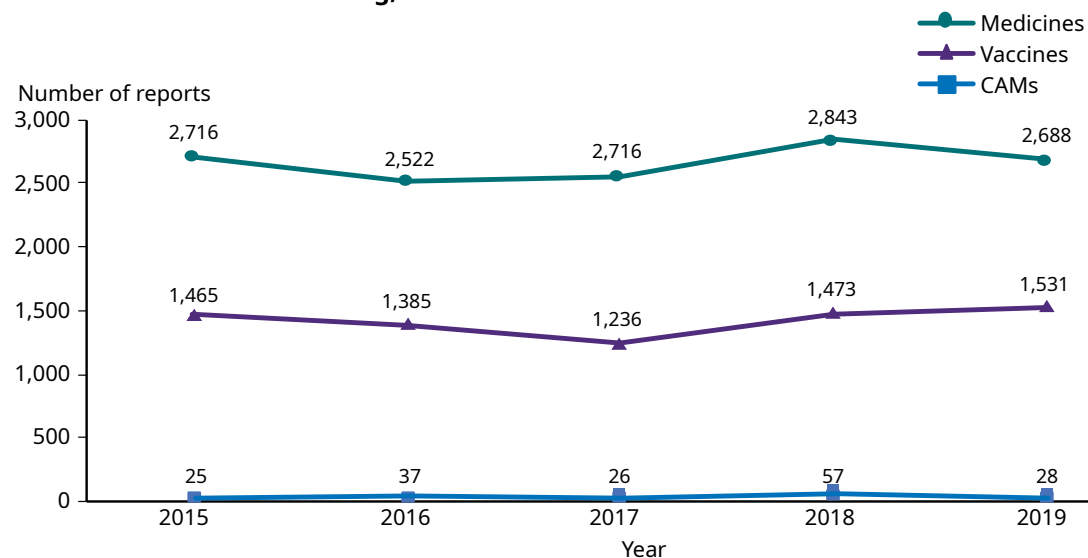
Adverse reaction reporting in New Zealand – 2019

Thank you to everyone who submitted reports of suspected adverse reactions during 2019. You are making an important contribution to the safety monitoring of medicines in New Zealand. Reporting suspected adverse drug reactions enables Medsafe to quickly identify and respond to emerging medicine safety issues.

What is being reported?

In 2019, the Centre for Adverse Reactions Monitoring (CARM) received a total of 4,247 reports of suspected adverse reactions. These included 2,688 reports associated with medicines, 1,531 reports associated with vaccines and 28 reports associated with complementary or alternative medicines (CAMs). The reporting pattern is similar to previous years (Figure 1).

Figure 1: Adverse reactions to medicines, vaccines and CAMs, reported to the Centre for Adverse Reactions Monitoring, 2015–2019



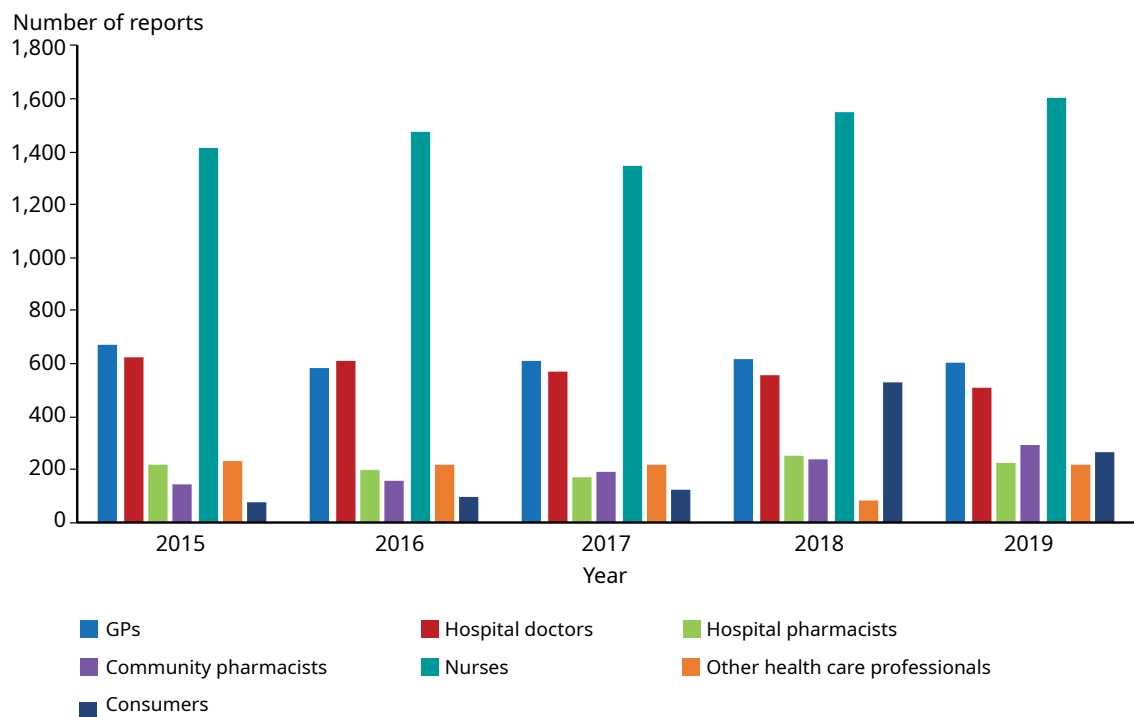
Of all reports received in 2019, 18.7 percent were considered serious. Serious reports accounted for 27.7 percent of medicine reports, 2.8 percent of vaccine reports and 28.6 percent of CAM reports. A serious adverse reaction is defined as any reaction that results in death or is life-threatening, causes or prolongs hospitalisation, results in persistent or significant disability/incapacity, is a congenital abnormality or is a medically important event.

You can find more information about suspected adverse reactions reported in New Zealand on the Medsafe website, using the Suspected Medicines Adverse Reaction Search (SMARS): medsafe.govt.nz/Projects/B1/ADRSearch.asp

Who is reporting?

Anyone can submit a report. Figure 2 shows the number of reports received from health care professionals and consumers during the last five years. Nurses continue to submit the most reports.

Figure 2: Number of reports received from health care professionals and consumers, 2015–2019



Reporting is easiest online

Please continue to report any suspected adverse reactions to medicines, vaccines or CAMs to CARM. Online reporting is easiest: nzphvc.otago.ac.nz/reporting/

Other ways of reporting include:

- electronic reporting through GP Practice Management Systems
- using the Apple iOS app on your iPhone or iPad (download from nzphvc.otago.ac.nz/app/)
- contacting CARM by phone on 03 479 7247 or emailing carmnz@otago.ac.nz

Influenza vaccine: Looking back on 2019 and what to expect this year

Key messages

- There are changes to the strains contained in quadrivalent influenza vaccines this year (2020) compared to last year.
- There are also changes to the funded influenza vaccines:
 - eligible children aged under 3 years will receive the Afluria Quad Junior vaccine, which contains 7.5 mcg of each vaccine strain per 0.25 mL dose
 - eligible people aged 3 years and older will receive Afluria Quad, which contains 15 mcg of each vaccine strain per 0.5 mL dose.
- Local injection site reactions were the most commonly reported group of adverse reactions during 2019.

About one in four New Zealanders are infected with influenza each year and a proportion of these are hospitalised¹. This has a significant impact on our health services.

Immunisation remains the best defence against influenza.

Looking back on 2019

Influvac Tetra was the funded vaccine for people aged 3 years and older and Fluarix Tetra was the funded vaccine for children aged under 3 years.

There were more than 1.35 million doses of influenza vaccine distributed in 2019, the highest number of doses ever delivered annually.

The Centre for Adverse Reactions Monitoring (CARM) received 229 suspected reports of adverse reactions to influenza vaccine in 2019 (Table 1), of which 2.6 percent were considered serious. A serious adverse reaction is defined as any reaction that results in death or is life-threatening, causes or prolongs hospitalisation, results in persistent or significant disability/incapacity, is a congenital abnormality or is a medically important event.

There were 550 adverse reactions described in the reports. The most commonly reported adverse reactions were injection site inflammation, arm pain, dizziness, headache and pruritus (Table 2).

The majority of reports in 2019 were submitted by nurses (68.6 percent), followed by GPs (14.9 percent) and pharmacists (9.2 percent). This reporter pattern is similar to previous years.

Table 1: Number of reports of adverse events following influenza vaccination received by the Centre for Adverse Reactions Monitoring and number of influenza vaccine doses distributed, 2015–2019

	2015	2016	2017	2018	2019
Number of adverse event reports following influenza vaccination	241	212	191	232	229
Influenza vaccine doses distributed ^a	1,211,152	1,245,934	1,217,169 ^b	1,317,197	1,355,666
Estimated reporting rate per 100,000 doses	19.9	17.0	15.7	17.6	16.9

Notes:

a The number of doses distributed is not equal to the number of people who received the vaccine.

b The 2017 influenza vaccine distribution figures were updated in 2018 and differ slightly from those previously published in *Prescriber Update* (medsafe.govt.nz/profs/PUArticles/March2018/seasonal-flu-vaccine-spontaneous-reports.htm). The estimated reporting rate is unchanged.

Table 2: Top five reported suspected adverse reactions for seasonal influenza vaccines, 2019

Adverse reaction	Number	Percentage of total reactions (n=550)	Percentage of total reports (n=229)
Injection site inflammation	59	10.7	25.8
Arm pain	22	4.0	9.6
Dizziness	20	3.6	8.7
Headache	17	3.1	7.4
Pruritus	17	3.1	7.4

What to expect this year

The following strains will be included in quadrivalent influenza vaccines this year, as recommended by the World Health Organization²:

- A/Brisbane/02/2018 (H1N1)pdm09-like virus
- A/South Australia/34/2019 (H3N2)-like virus
- B/Washington/02/2019-like (B/Victoria lineage) virus
- B/Phuket/3073/2013-like (B/Yamagata lineage) virus.

The funded influenza vaccine is changing in 2020. Eligible children aged under 3 years will receive the Afluria Quad Junior vaccine, which contains 7.5 mcg of each vaccine strain per 0.25 mL dose (total antigen content is 30 mcg/0.25 mL)³. Eligible adults will receive Afluria Quad, which contains 15 mcg of each vaccine strain per 0.5 mL dose (total antigen content is 60 mcg/0.5 mL).

Help track influenza across New Zealand by joining FluTracking: info.flutracking.net

References

1. Huang S (on behalf of the SHIVERS investigation team). 2016. *Key findings – SHIVERS. Presented at the 2016 New Zealand Influenza Symposium, 2 November 2016* (updated January 2017). URL: immune.org.nz/sites/default/files/Conferences/2016/NZIS2016/8%201310%2020161102%20NZIS%20SHIVERSRevisedJan2017.pdf (accessed 28 January 2020).
2. Medsafe. 2019. *Influenza vaccine composition* 17 October 2019. URL: medsafe.govt.nz/regulatory/flu.asp (accessed 16 January 2020).
3. PHARMAC. 2020. *Pharmaceutical Schedule* February 2020 27(0): 265–6. URL: pharmac.govt.nz/2020/02/01/Schedule.pdf (accessed 28 January 2020).

Correction: Some medicines increase serum creatinine without affecting glomerular function

The December 2019 edition of *Prescriber Update* contained an article about medicines that can increase serum creatinine without affecting glomerular function¹.

Amantadine, cobicistat and olaparib were included as currently approved medicines that have been reported to compete with the active secretion of creatinine. Dolutegravir was not included in this list.

The article on the Medsafe website has been updated to include dolutegravir.

Reference

1. Medsafe. 2019. Some medicines increase serum creatinine without affecting glomerular function. *Prescriber Update* 40(4): 91–2. URL: medsafe.govt.nz/profs/PUArticles/December2019/Some-medicines-increase-serum-creatinine-without-affecting-glomerular-function.htm (accessed 8 January 2020).

Recent approvals of medicines containing a new active ingredient

For period 16 October 2019 to 15 January 2020.

Trade Name (Active ingredient)	Dose form and strength(s)	Therapeutic area
Besponsa (inotuzumab osogamicin)	Powder for injection 1 mg	Acute lymphoblastic leukaemia
Eryland (apalutamide)	Film coated tablet 60 mg	Prostate cancer
Odomzo (sonidegib)	Capsule 200 mg	Basal cell carcinoma
Rydapt (midostaurin)	Soft gelatin capsule 25 mg	Acute myeloid leukaemia, aggressive systemic mastocytosis, systemic mastocytosis with associated haematological neoplasms, mast cell leukaemia
Spravato (esketamine)	Nasal spray solution 140 mg/mL	Depression

See the Medsafe website for more information about these medicines (medsafe.govt.nz/regulatory/DbSearch.asp). Data sheets of currently marketed medicines are also available (medsafe.govt.nz/Medicines/infoSearch.asp).

Quarterly summary of recent safety communications

The table below is a summary of recent safety communications to health care professionals and consumers, published on the Medsafe website (medsafe.govt.nz).

Date	Communication	Topic
23/01/2020	Monitoring	Update – Everet (levetiracetam) – supply and potential seizure control issues for patients
23/01/2020	Monitoring	Update – Dolutegravir and the possible risk of neural tube defects when taken early in pregnancy
21/01/2020	Dear Healthcare Professional Letter	Gardasil 9 – Issue with ‘tear-off’ labels for Gardasil 9 vaccine (PDF 43 KB, 1 page)
14/01/2020	Dear Healthcare Professional Letter	Accuretic – Supply in alternative (Canadian) artwork to New Zealand (PDF 490 KB, 2 pages)
08/01/2020	Monitoring	M² Update – Risk of infections with Prolia (denosumab)
08/01/2020	Monitoring	M² Update – Tramadol and opioid effects in breastfeeding babies
20/12/2019	Monitoring	Update on suspected adverse reaction reports to lamotrigine after changing brands
19/12/2019	Alert	EpiPen® Jr 150 mcg Adrenaline (epinephrine) Auto-Injector containing trace levels of Pralidoxime
17/12/2019	Dear Healthcare Professional Letter	Tivicay and dolutegravir containing regimens – updated information (PDF 134 KB, 2 pages)
9/12/2019	Monitoring	M² Update – Isotretinoin and Obsessive Compulsive Disorder (OCD)

Hormone replacement therapy (HRT) reminder

Remember to prescribe hormone replacement therapy (HRT) at the lowest effective dose for the shortest duration possible. Review the need for continued use of HRT at least once every year.

A recent meta-analysis published in *The Lancet* confirmed an increased risk of breast cancer during treatment with all forms of HRT, except low-dose vaginal estrogen preparations¹. This study found the risk of breast cancer increases with longer duration of HRT use. In addition, after stopping HRT, some excess risk persisted for more than 10 years.

HRT also increases the risk of venous thromboembolism and stroke².

Carefully weigh the benefits and risks of treatment for each patient before initiating treatment and at regular intervals (at least yearly).

References

1. Collaborative Group on Hormonal Factors in Breast Cancer. 2019. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. *Lancet* 394(10204): 1159–68. DOI: 10.1016/S0140-6736(19)31709-X (accessed 8 January 2020).
2. Boardman HMP, Hartley L, Eisinga A, et al. Hormone therapy for preventing cardiovascular disease in post-menopausal women (Review). *Cochrane Database Syst Rev* 2015, Issue 3, Art. No. CD002229. DOI: 10.1002/14651858.CD002229.pub4 (accessed 28 January 2020).

MARC's remarks: December 2019 meeting

The Medicines Adverse Reactions Committee (MARC) met on 5 December 2019 to discuss a number of medicine-related safety issues.

Based on a case reported to the Centre for Adverse Reactions Monitoring (CARM ID 133836), where a young patient developed hyponatraemia and tonic/clonic convulsions after using **desmopressin**, the MARC recommended further communication on the need for concomitant fluid reduction with desmopressin. For more information, see the Gathering Knowledge article on page 14 of this edition of *Prescriber Update*.

The MARC discussed the benefits of use and risks of harm of the cough suppressant **pholcodine**. The MARC considered that the benefit-risk balance is marginal, but there is currently insufficient evidence to indicate an unfavourable benefit-risk balance. The MARC recommended the Medicines Classification Committee consider reclassifying pholcodine to a more restricted classification.

The MARC discussed the use of **direct-acting oral anticoagulants** and the risk of recurrent thrombotic events. The MARC determined that there is currently insufficient evidence of a rebound effect.

The MARC discussed the use of **cyproterone acetate** and the risk of hepatic toxicity. The MARC recommended that data sheets should be updated to clarify that hepatic toxicity is not gender specific and can happen at doses lower than the 200–300 mg currently described in the data sheets.

The potential drug-drug interaction between **capecitabine** and **proton pump inhibitors** (PPIs) was discussed. The proposed mechanism of the interaction is that PPIs increase gastric pH, which may reduce the dissolution and absorption of capecitabine. The MARC recommended data sheet updates to outline this potential interaction and recommended communication with oncologists to inform them of the MARC's discussion on this topic.

See the Medsafe website for the MARC meeting minutes (medsafe.govt.nz/profs/MARC/Minutes.asp) and the reports presented to the MARC (medsafe.govt.nz/committees/MARC/Reports.asp).

We need your help!



Please send your reports to CARM (nzphvc.otago.ac.nz/reporting/) for the potential safety issues* listed in the table below.

Medicine	Potential safety issue	Active monitoring ends
Dabigatran	Vasculitis	14 May 2020

- **M²** (Medicines Monitoring) is a Medsafe scheme designed to collect more information on potential safety signals for specific medicines.
- Please send your report to CARM (as for any suspected adverse reaction). This can be done even if the reaction happened some time ago. Please include as much information as possible as this helps the medical assessors at CARM to investigate whether the medicine caused the reaction.
- For further information about **M²**, see the Medsafe website (medsafe.govt.nz/profs/M2MedicinesMonitoring.asp).

* The appearance of a possible safety issue in this scheme does not mean Medsafe and CARM have concluded that this medicine causes the reaction.

Gathering knowledge from adverse reaction reports: March 2020

Adverse reaction reporting is an important component of medicine safety monitoring. Case reports can highlight significant safety issues concerning therapeutic products and their use.

The table below presents a selection of recent informative cases from the Centre for Adverse Reactions Monitoring (CARM) database.

Case details ^a	Reaction description and data sheet information ^b
CARM ID: 132502 Age: 57 Gender: Female Medicine(s): Dapagliflozin Reaction(s): Urinary tract infection, pyelonephritis	<p>A female patient taking dapagliflozin for diabetes experienced urinary tract infection (UTI) symptoms for a week and then developed pyelonephritis with high fevers and rigors. She was hospitalised and the dapagliflozin stopped. The patient was reported to have had a UTI 3 months previously, also while taking dapagliflozin.</p> <p>UTI and pyelonephritis are described in the Forxiga data sheet (medsafe.govt.nz/profs/Datasheet/f/forxigatab.pdf).</p> <p>Urinary glucose excretion may be associated with an increased risk of urinary tract infection. Evaluate patients for signs and symptoms and treat promptly, if indicated. Temporary interruption of dapagliflozin should be considered when treating pyelonephritis or urosepsis. Discontinuation of Forxiga may be considered in cases of recurrent UTIs.</p>

Case details ^a	Reaction description and data sheet information ^b
<p>CARM ID: 133295</p> <p>Age: 19</p> <p>Gender: Female</p> <p>Medicine(s): Valaciclovir</p> <p>Reaction(s): Acute kidney injury, abdominal pain</p>	<p>A female patient taking valaciclovir developed abdominal pain. Upon assessment, she was diagnosed with acute kidney injury and admitted to hospital. The symptoms resolved spontaneously.</p> <p>Abdominal discomfort, renal impairment and acute renal failure are listed in the Valclovir data sheet (medsafe.govt.nz/profs/Datasheet/v/vaclovirtab.pdf).</p>
<p>CARM ID: 133836</p> <p>Age: 8</p> <p>Gender: Male</p> <p>Medicine(s): Desmopressin</p> <p>Reaction(s): Hyponatraemia, generalised tonic-clonic seizure</p>	<p>An 8-year-old patient had a suspected hyponatremic seizure approximately one month after starting treatment with desmopressin.</p> <p>Hyponatremia and convulsions are listed in the Desmopressin PH&T data sheet (medsafe.govt.nz/profs/Datasheet/d/DesmopressinPHNasalspray.pdf).</p> <p>When used for enuresis, fluid intake must be limited to a minimum for 1 hour before until 8 hours after administration.</p> <p>Treatment without concomitant reduction of fluid intake may lead to water retention/hyponatremia with accompanying signs and symptoms (headache, nausea/vomiting, decreased serum sodium, weight gain and in serious cases, convulsions).</p>
<p>CARM ID: 134398</p> <p>Age: 66</p> <p>Gender: Female</p> <p>Medicine(s): Bevacizumab</p> <p>Reaction(s): Endophthalmitis, visual impairment</p>	<p>A female patient reported loss of vision 2 days after intravitreal injection of bevacizumab. She was diagnosed with endophthalmitis and treated with steroids and antibiotics, but the visual impairment remained.</p> <p>Although bevacizumab (Avastin) is funded for intraocular use, this is not an approved indication.</p> <p>The Avastin data sheet states that individual cases and clusters of serious ocular adverse events have been reported following unapproved intravitreal use of Avastin compounded from vials approved for intravenous administration in cancer patients. Some of these events have resulted in various degrees of visual loss, including permanent blindness (medsafe.govt.nz/profs/Datasheet/a/Avastininf.pdf).</p> <p>These reactions can also occur with medicines approved for intravitreal treatment of macular degeneration.</p>

Case details ^a	Reaction description and data sheet information ^b
CARM ID: 134937 Age: 32 Gender: Male Medicine(s): Ciclosporin, posaconazole Reaction(s): Drug interaction, drug level increased, generalised tonic-clonic seizure, renal impairment, thrombocytopenia	<p>A 32-year-old transplant patient taking ciclosporin and posaconazole experienced a drug interaction and symptoms of ciclosporin toxicity including seizure, renal impairment and thrombocytopenia.</p> <p>Ciclosporin is metabolised by CYP3A4 and posaconazole is a CYP3A4 inhibitor.</p> <p>For transplant patients who cannot avoid concomitant use of medicines known to interact with ciclosporin, the Neoral data sheet recommends frequent measurement of ciclosporin levels and dose adjustment if necessary, particularly during introduction or withdrawal of the co-administered medicine. For non-transplant patients taking a concomitant medicine known to increase ciclosporin levels, frequent assessment of renal function and careful monitoring of ciclosporin-related side effects may be more appropriate than blood level measurement (medsafe.govt.nz/profs/Datasheet/n/Neoralsolcap.pdf).</p>

Notes:

- Only the medicines suspected to have caused the reaction are listed in the table.
- If the suspect medicine's brand name is not described in the report to CARM, only the data sheet for the funded medicine is included in the table.

Information about suspected adverse reactions reported to CARM is available on the Medsafe website using the Suspected Medicines Adverse Reaction Search (SMARS) (medsafe.govt.nz/Projects/B1/ADRSearch.asp).

By selecting the ingredient of a medicine, you can find out:

- the number of reports and suspected adverse reactions for that ingredient. The suspected reactions are grouped by body system or organs (Summary report)
- single case reports, listing the medicines involved that contain the ingredient and the suspected adverse reactions (Detail report).

Interacting elements – zinc-induced copper deficiency

Zinc may inhibit the absorption of copper, leading to reduced copper levels, and potentially copper deficiency¹. This deficiency is due to an interaction between zinc and copper, where zinc inhibits the intestinal absorption of copper².

Copper is an essential trace element and deficiency may result in anaemia, leucopenia, neutropenia and thrombocytopenia³. Early diagnosis is important to avoid the possibility of developing disabling and frequently irreversible neurological symptoms⁴.

In New Zealand, Zincaps capsules are indicated for use in adults as a zinc supplement. The Zincaps data sheet was recently updated to include the zinc and copper interaction (medsafe.govt.nz/profs/Datasheet/z/Zincaps.pdf). The data sheet also has information about other medicines that interact with zinc.

The risk of copper deficiency may be greater with long-term treatment (eg, if zinc deficiency is no longer present) and/or with higher doses of zinc¹.

When treating copper-deficient patients, concomitant zinc should be administered with caution.

References

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4. Duncan A, Yacoubian C, Watson N, et al. 2015. The risk of copper deficiency in patients prescribed zinc supplements. *Journal of Clinical Pathology* 68(9): 723–5. DOI: 10.1136/jclinpath-2014-202837 (accessed 10 February 2020).

The Medsafe Files – Episode 13: Medical device adverse event reporting

Key messages

- A key part of the post-market regulation of medical devices relies on adverse events and quality issues relating to devices being reported to Medsafe.
- Anyone can report an issue associated with a medical device.
- Medsafe uses adverse event reporting as a tool to investigate issues with medical devices. Medsafe investigations contribute to the safer use of medical devices in New Zealand.

Medsafe's role in regulating medical devices focuses on post-market activities because there is no pre-market approval of devices. To do this, we use information received by international regulators, suppliers of devices, health care professionals and patients.

Medsafe has an important role in post-market regulation of medical devices

As with medicines, medical devices are defined in and regulated under the Medicines Act 1981. However, unlike medicines, there is no pre-market approval system for medical devices. This means that devices are not assessed by Medsafe in terms of quality, safety, efficacy or performance before they are distributed in New Zealand.

It is, however, a mandatory requirement that suppliers of medical devices notify their products to the WAND notification database. If there is a medical device safety issue, we use information in the WAND database to identify all suppliers of that device.

Medical device adverse event reports provide us with important information

A key source of information is medical device adverse event reports. These reports help us to identify potential issues with devices and to investigate and take regulatory action when needed.

Our regulatory action can result in a corrective action being implemented to address a device defect, an update to device instructions for use, publication of safety alerts on our website and recalls of devices from the market.

We don't take direct action on every report received, however all reports are important and useful in identifying trends. In addition, there are some issues that do not need to be reported to us, for example, improper use of the device. See our website for more information (medsafe.govt.nz/regulatory/DevicesNew/9AdverseEvent.asp).

Anyone can report an issue relating to a medical device

Anyone can report a medical device adverse event. Reporting forms are available on our website.

If a patient reports an adverse event relating to a medical device to you, as their health care professional, we strongly encourage you to report this to us. Health care professionals are often able to provide information which can help to identify the device in question and provide clinical context.

Patient information remains confidential to Medsafe.

Additional information

- For more information about medical device adverse event reporting, and to download the reporting forms: medsafe.govt.nz/regulatory/DevicesNew/9AdverseEvent.asp
- For an explanation of the WAND database: medsafe.govt.nz/regulatory/DevicesNew/3-2Explanation.asp

***Hearing and Responding to the Stories of Survivors of Surgical Mesh* report: Update from the Ministry of Health**

Key messages

- For those who experience complications from surgical mesh, the impact can be significant and life-changing.
- Patients have the right to be fully informed, make informed choices and give informed consent. This report highlights the importance of health care professionals ensuring robust informed consent process and being responsive to concerns or complications following surgery.

The report *Hearing and Responding to the Stories of Survivors of Surgical Mesh*, commissioned by the Ministry of Health, was released on 12 December 2019. The report summarises the themes that emerged from a restorative justice process undertaken to listen to the stories of New Zealanders affected by surgical mesh.

You can download the report from the Ministry of Health website: health.govt.nz/publication/hearing-and-responding-stories-survivors-surgical-mesh

The report highlights the severity of the harm and the impact on the lives of those who experience complications from surgical mesh. Mesh injured New Zealanders have described life-changing physical and psychosocial harms including losses to their physical wellbeing, relationships, identity, employment and financial status. They also expressed a loss of trust in health care providers and institutions.

Consumers and health care professionals identified several major needs to address surgical mesh harm. The report groups these needs into the following workstreams:

- credentialling of surgeons
- specialist multidisciplinary mesh services

- informed consent
- safety culture and systems
- acknowledgement of harm
- responding to mesh harm both now and in the future.

Actions to address these needs are described in the report. The Ministry is committed to working with other agencies to progress these actions, supporting those who have been affected and minimising future harm.

See also the article on medical device adverse event reporting on page 17 of this edition of *Prescriber Update*.

Medicinal Cannabis Scheme: Update from the Ministry of Health

Key messages

- The Misuse of Drugs (Medicinal Cannabis) Regulations 2019 will come into effect on 1 April 2020, enabling the Medicinal Cannabis Scheme (the Scheme) to become operational. A Medicinal Cannabis Agency is being established to administer the Scheme.
- A 6-month transition period from 1 April 2020 until 1 October 2020, allowing current prescribing and supply rules to continue, will ensure patients can continue to access medicinal cannabis products currently being prescribed to them.
- From 1 April 2020, all medical practitioners will be able to prescribe medicinal cannabis products consented for distribution (approved) under the Medicines Act 1981 (ie, Sativex). Ministerial approval and specialist recommendation will no longer be required for these products.
- Once an unapproved medicinal cannabis product has been assessed by the Medicinal Cannabis Agency as meeting the quality standards, then all medical practitioners will be able to prescribe that product. Ministerial approval and specialist recommendation will not be required.

This article has been provided by the Ministry of Health. It provides an overview of the access of unapproved medicinal cannabis products under the new Medicinal Cannabis Scheme, when the suppliers of these products do not seek consent for distribution (approval) under the Medicines Act 1981.

The Scheme requires products manufactured from the *Cannabis* plant to meet minimum quality standards, in addition to Medicines Act 1981 requirements for unapproved medicines and Misuse of Drugs Act 1975 requirements for controlled drugs.

Note that the minimum quality standard does not include an assessment of safety and efficacy. For details of what is included in the minimum quality standard, please see the Ministry of Health website ([health.govt.nz/our-work/regulation-health-and-disability-system/medicinal-cannabis-scheme/medicinal-cannabis-regulation/upcoming-medicinal-cannabis-regulatory-information/medicinal-cannabis-minimum-quality-standard](https://www.health.govt.nz/our-work/regulation-health-and-disability-system/medicinal-cannabis-scheme/medicinal-cannabis-regulation/upcoming-medicinal-cannabis-regulatory-information/medicinal-cannabis-minimum-quality-standard)).

Medicinal Cannabis Scheme

On 18 December 2019, the government passed the Misuse of Drugs (Medicinal Cannabis) Regulations 2019 to enable the Medicinal Cannabis Scheme. A Medicinal Cannabis Agency will be operational from 1 April 2020 to administer the Scheme.

The regulations enable the establishment of a licensing regime for the cultivation of cannabis for a medicinal purpose and the manufacture and supply of medicinal cannabis products (MCPs) in New Zealand. The regulations also set out a minimum quality standard that all medicinal cannabis products must meet. All medicinal cannabis products must be manufactured under Good Manufacturing Practice (GMP). These requirements will provide prescribers confidence in the quality of the product, which cannot be ensured for all other unapproved medicines.

From 1 April 2020 there will be a 6-month transition period where the supply of MCPs already available will continue under current licences to ensure that patient access is maintained. Current suppliers of MCPs will have until 1 October 2020 to submit their existing product for an assessment against the medicinal cannabis quality standard.

Products that have already obtained Medsafe consent for distribution under the Medicines Act 1981 (ie, Sativex) and any future product which obtains this, are not required to meet the medicinal cannabis quality standard (see below).

Changes to prescribing

The regulations introduce significant changes to the prescribing of MCPs in order to minimise barriers and improve access. Once a MCP has been assessed by the Medicinal Cannabis Agency and has been verified as meeting the quality standard, it can be prescribed by any medical practitioner. Ministerial approval and specialist recommendation will not be required.

We expect suppliers of already available products to apply for assessment of their products during the 6-month transition period so that supply can continue after 1 October 2020. The Medicinal Cannabis Agency will be accepting applications from companies for product assessments from 1 April 2020.

A list of MCPs which meet the quality standard will be made available to prescribers and other health care professionals.

Prescribing requirements

MCPs, except cannabidiol (CBD) products, are controlled drugs under the Misuse of Drugs Act 1975. CBD products are prescription medicines under the Medicines Act 1981.

With the exception of Sativex¹ (see below), all MCPs available in the immediate future will be unapproved medicines – that is, they will not have consent for distribution under the Medicines Act 1981. Prescribers should be familiar with the requirements for prescribing unapproved medicines and Medsafe guidance on the topic².

Products should be prescribed by brand and prescriptions should not permit generic substitution. A medicinal cannabis product must **not** be in a form intended for smoking, a food or be a sterile dosage form (eg, eye drops).

Cannabidiol (CBD) products

CBD products primarily contain cannabidiol and little to no tetrahydrocannabinol (THC) and other related psychoactive substances (Section 2A of the Misuse of Drugs Act 1975 has a specific definition of a CBD product³).

These products will be in a pharmaceutical dosage form such as a capsule or oral liquid.

CBD products which are **currently available** can continue to be prescribed and supplied after 1 April 2020. However, *suppliers* will need to provide evidence of products meeting the quality standards to continue supplying them after 1 October 2020.

Other medicinal cannabis products (excluding CBD products)

Because other MCPs (ie, excluding CBD products) are controlled drugs, additional requirements for prescribing controlled drugs apply, including handwritten prescriptions on a controlled drug prescription form for a quantity not exceeding a 1-month supply.

Other MCPs may be in a pharmaceutical dosage form or as dried flower intended for vapourisation.

Products which do not meet the minimum quality standard

If a medicinal cannabis product does not meet the minimum quality standard or has not yet been assessed by the Medicinal Cannabis Agency there will still be pathways available to prescribe it.

- CBD products will only be able to be prescribed by a medical practitioner and imported directly for the named patient by the medical practitioner or a pharmacy on behalf of the medical practitioner.
- Other medicinal cannabis products (ie, controlled drugs) that have not met the quality standard will only be able to be prescribed with Ministerial approval and specialist recommendation. They will have to be imported directly by the medical practitioner or pharmacy on behalf of the medical practitioner to supply to the named patient.

Ministerial approval to prescribe for named patients, obtained prior to 1 April 2020, will continue to be valid until it expires.

Products consented for distribution (approved) under the Medicines Act 1981

Any medicinal cannabis product that gains consent to distribute under the Medicines Act 1981 is required to meet Good Manufacturing Practice (GMP) and will have been assessed and met the standards of quality that apply to medicines. These products will therefore not be required to meet the medicinal cannabis quality standard.

Sativex is currently the only medicinal cannabis product that has consent for distribution under the Medicines Act 1981 – meaning it has been assessed for safety and efficacy for its approved indication, in addition to manufacturing quality. From 1 April 2020, Sativex can be prescribed without Ministerial approval or specialist recommendation for any indication (ie, both on-label and off-label).

More information

For more information on the Scheme, see the Ministry of Health website: health.govt.nz/our-work/regulation-health-and-disability-system/medicinal-cannabis-scheme.

Further information and guidance will be published as it becomes available.

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