

Prescriber Update

Vol. 42 No. 2

June 2021

www.medsafe.govt.nz

ISSN 1179-075X (online)

Contents

Colchicine: painful insights from recent poisoning data in New Zealand	14
Spotlight on Comirnaty vaccine	16
Anaphylaxis following vaccination: focus on Comirnaty	18
MARC's remarks: March 2021 meeting	20
M Medicines Monitoring – Pregabalin	21
Prednisone treatment – follow dosing recommendations	21
Quarterly summary of recent safety communications	22
Small increased risk of postpartum haemorrhage with use of serotonergic antidepressants close to delivery	23
Gathering knowledge from adverse reaction reports: June 2021	24
Nitrofurantoin: prescribe by brand	26
The paradox of opioid -induced hyperalgesia	27
Recent approvals: new active ingredients or new indications	29

Colchicine: painful insights from recent poisoning data in New Zealand

Key messages

- Colchicine has a narrow therapeutic index. An overdose of colchicine carries a high risk of fatality and there are no effective treatments available for severe colchicine poisoning.
- National Poisons Centre data shows the most common reasons given for colchicine poisoning are child exploratory behaviour, followed by therapeutic error.
- Communicate clearly with patients about the correct dose, safe storage and appropriate disposal of unused colchicine to help reduce the risk of harm.

Colchicine indications and dosing¹

Colchicine is indicated for the treatment of acute gout when nonsteroidal anti-inflammatory drugs are contraindicated, ineffective or not tolerated.

The approved dose for treatment of acute gout is 1 mg (two tablets) at the first sign of the flare, followed by 0.5 mg (one tablet) one hour later. Higher doses have not been found to be more effective. The maximum recommended dose for treatment of acute gout is 1.5 mg (three tablets) over a one hour period. A course of colchicine should not be repeated within three days.

Some clinical guidelines may refer to unapproved dosing schedules for colchicine. See the Medsafe information about [unapproved use of medicines](#), particularly the requirement for patient consent.

Colchicine can be fatal in overdose

Colchicine has a narrow therapeutic index. The separation between therapeutic and toxic doses is not well defined.²

Case reports and case series data suggest a dose-dependent fatality risk that increases dramatically over a narrow colchicine dose range from 0.5–1 mg/kg when taken over short time periods. Doses well under 0.5 mg/kg (and as low as 0.18 mg/kg) have been associated with deaths in New Zealand, with multiple deaths involving accidental overdoses.³

Fatal colchicine toxicity has occurred in adults at doses as low as 7 mg when taken for a therapeutic purpose.^{1,2}

The risk of toxicity is increased by coadministration with medicines that inhibit cytochrome P450 3A4 or P-glycoprotein, and comorbidities such as renal or hepatic impairment.¹

Colchicine toxicity is an extension of its mechanism of action. Colchicine inhibits the formation of microtubules, affecting cell division in all cell types of the body, which accounts for both the therapeutic effects and the multi-organ toxicity seen in colchicine poisoning.²

There is no antidote for colchicine poisoning. Treatment is usually supportive and involves early administration of activated charcoal.¹ Colchicine toxicity has a high mortality rate.²

Poisoning from colchicine in New Zealand

From 1 January 2016 to 14 January 2021, the National Poisons Centre (NPC) received 56 unique cases related to colchicine poisoning. Māori and Pacific peoples comprised 34 percent of the poisoning cases, 13 percent were European, and the remainder were of unknown ethnicity.

Forty-three percent of the cases were aged 1 to 4 years, and 36 percent of the cases were aged 20 to 75 years. Table 1 below shows the number of colchicine poisoning incidents per year and the reasons.

The NPC provided the following insights into the poisonings.

- Child exploratory behaviour: 43 percent of all colchicine cases were toddlers and young children (aged 1 to 4 years) gaining unsupervised access to the medicine. Due to the small size of children, as little as one or two tablets may be of concern for toxicity – prompting referral for medical assessment.
- Therapeutic error: 35 percent of cases were adults who were exposed to a supratherapeutic dose. These exposures may be due to patients misunderstanding how to take colchicine appropriately or trying to get further therapeutic effect to ease symptoms of gout.
- Intentional self-poisoning: any intentional exposure to colchicine poses a medical emergency, given the severity of toxicity and high fatality rate associated with colchicine overdose.

Table 1: Number of colchicine poisoning incidents and reasons as reported to the National Poisons Centre, New Zealand, 2016 to 2021^{a,b}

Reason	Number per year						Total	
	2016	2017	2018	2019	2020	2021 ^b	No.	%
Child exploratory behaviour	3	11	1	4	5	0	24	43
Intentional	1	0	3	2	5	1	12	21
Therapeutic error	1	5	1	3	5	0	15	27
Unintentional	0	0	0	3	1	0	4	7
Unknown	0	0	0	0	1	0	1	2
Total	5	16	5	12	17	1	56	100

Source: National Poisons Centre

Notes:

- The data does not capture all harmful or potentially harmful colchicine poisonings that occurred during the specified period in New Zealand, as contacting the National Poisons Centre is voluntary.
- Data to 14 January 2021.

Reducing harm from colchicine in the community

- Communicate with patients about the importance of storing medicines out of sight and reach of children.
- Encourage patients to return unused or expired medicines to their local pharmacy for appropriate disposal.
- When dispensing colchicine, discuss with the patient if a child resistant closure would be acceptable, taking into account patient and whānau factors.
- Ensure patients know when and how to take colchicine. [Health Navigator](#) is a useful consumer resource, with patient information leaflets about colchicine.
- If a patient experiences colchicine poisoning, contact the National Poisons Centre on 0800 764 766 for consultation with a clinical toxicologist for risk assessment and recommendations on treatment. This service is available 24/7.

More information

See the following *Prescriber Update* articles about colchicine:

- [Spotlight on colchicine](#) – March 2018
- [Keeping patients informed about colchicine use](#) – December 2014
- [Colchicine: Beware of toxicity and interactions](#) – March 2011.

See also the [Medsafe consumer information leaflet](#), Medicines for gout.

References

1. Pharmacy Retailing t/a Healthcare Logistics. 2020. *Colgout New Zealand Data Sheet* November 2020
URL: medsafe.govt.nz/profs/datasheet/c/Colgouttab.pdf (accessed 30 March 2021).
2. Finkelstein Y AS, Hutson JR, Juurlink DN, et al. 2010. Colchicine poisoning: the dark side of an ancient drug. *Clinical Toxicology* 48(5): 407-14. DOI: <https://doi.org/10.3109/15563650.2010.495348> (accessed 30 March 2021).
3. Jayaprakash V, Ansell G, Galler D. 2007. Colchicine overdose: the devil is in the detail. *New Zealand Medical Journal* 120(1248): U2402. PMID: 17277818 (accessed 19 April 2021).

Spotlight on Comirnaty vaccine

Key messages

- Comirnaty vaccine has provisional approval for use in individuals aged 16 years and older, based on a favourable benefit risk profile.
- The known reactions are detailed in the data sheet and are those typically associated with vaccines.
- Please continue to report any adverse events following immunisation.

Introduction

Comirnaty vaccine, manufactured by Pfizer/BioNTech, is an mRNA vaccine indicated for the active immunisation against COVID-19 infection caused by SARS-CoV-2 in individuals aged 16 years and older.¹ The vaccine has provisional approval, granted under section 23 of the Medicines Act 1981.

Comirnaty is the first vaccine using mRNA technology to be used in New Zealand. The mRNA codes for the spike protein of the SARS-CoV-2 virus. The mRNA is contained within lipid nanoparticles to help protect it from damage and deliver it into the cell. The cell then manufactures the spike protein, which then stimulates the immune system.

The fragility of the mRNA means that the vaccine has particular storage requirements and needs careful handling during vaccine dilution and administration.

Efficacy

Efficacy was evaluated in study C459001 – a multicentre, multinational, phase 1/2/3 randomised placebo-controlled observer-blind trial.² Subjects received two doses of vaccine 21 days apart. Efficacy was calculated based on the number of cases of SARS-CoV-2 infection seven days after the second dose. At the time of Medsafe provisional approval, the median follow-up time for subjects in the study was two months. For the primary efficacy endpoint of symptomatic COVID-19 infection, data from 18,198 vaccinated subjects and 18,325 subjects given placebo resulted in a vaccine efficacy of 95 percent (95% credible interval: 90.3–97.6). The long-term efficacy remains to be elucidated. Follow-up of subjects in study C459001 is scheduled for completion in 2023.

Missing information

A number of conditions were placed on the provisional approval of Comirnaty vaccine to address missing information from the application. These conditions are published on the Medsafe website, in the [Gazette notice](#) and the [Product/Application search entry](#).

In addition, the following have been identified in the [Risk Management Plan](#) as areas of missing information.

- Use in pregnancy and while breast feeding.
- Use in immunocompromised patients.
- Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders).
- Use in patients with autoimmune or inflammatory disorders.
- Interaction with other vaccines.
- Long-term safety data.

Ongoing studies and collection of real-world safety data will help address these information gaps, and the data sheet will be updated as needed. [See the Risk Management Plan](#) for more details.

The Australasian Society of Clinical Immunology and Allergy have issued guidance on [vaccination for patients with immunodeficiency or autoimmunity](#).

The Ministry of Health also publishes [advice for the health sector](#).

Safety

In the clinical trial, the most frequently reported adverse reactions were injection site pain, fatigue, headache, myalgia, chills, arthralgia, pyrexia and injection site swelling.² These adverse reactions are often called reactogenic events. There was a slightly higher incidence of reactogenic events after the second dose compared to the first dose in the clinical trial.

The full list of adverse reactions can be found in the [data sheet](#). Rare but important adverse reactions include anaphylaxis (see the article on page 18), hypersensitivity and acute peripheral facial paralysis.

The Australasian Society of Clinical Immunology and Allergy have issued guidance on [allergy and COVID-19 vaccination](#).

The inclusion of acute peripheral facial paralysis was based on an imbalance of cases in the clinical trial: four cases in subjects receiving vaccine and none in subjects given placebo.

[An overview of the reports](#) to the Centre for Adverse Reactions Monitoring (CARM) describing adverse events following immunisation (AEFI) is published on the Medsafe website.

New Zealand's COVID-19 Independent Safety Monitoring Board (CV-ISMB) is an independent expert advisory group on the safety of COVID-19 vaccines. The CV-ISMB meets regularly to review the available safety information, including AEFIs reported to CARM, and provides expert advice to CARM, Medsafe, the COVID-19 immunisation programme and the Ministry of Health.

Reporting

We have had a fantastic response from vaccinators and vaccinees reporting AEFI to CARM. [Please continue to report](#) any suspected AEFI for the Comirnaty vaccine.

References

1. Pfizer New Zealand Limited. 2021. *Comirnaty New Zealand Data Sheet* 22 March 2021. URL: medsafe.govt.nz/profs/Datasheet/c/comirnatyinj.pdf (accessed 8 April 2021).
2. Polack FP, Thomas SJ, Kitchen N, et al. 2020. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *New England Journal of Medicine* 383(27): 2603–15. DOI: 10.1056/NEJMoa2034577 (accessed 8 April 2021).

Anaphylaxis following vaccination: focus on Comirnaty

Key messages

- Anaphylaxis is a very rare adverse event that may occur following administration of any vaccine, including vaccines for COVID-19 infection, such as Comirnaty.
- COVID-19 vaccines must always be administered in a setting where anaphylaxis can be promptly identified and treated.
- Anyone receiving the Comirnaty vaccine should be closely observed for at least 20 minutes following vaccination, but individuals with risk factors for anaphylaxis should be observed for a minimum of 30 minutes.
- Intramuscular adrenaline is the first line treatment for anaphylaxis.
- **1:1000** adrenaline must be readily available at vaccination centres.
- Individuals should not receive Comirnaty if they have a history of allergic reactions to any of the vaccine ingredients or if they experience anaphylaxis after the first dose.

Anaphylaxis is a life-threatening allergic reaction that can occur very rarely following the administration of a vaccine.¹

The New Zealand roll-out of COVID-19 vaccines commenced on 20 February 2021. The vaccine currently available is Pfizer/BioNTech mRNA COVID-19 vaccine (Comirnaty). There have been reports of suspected anaphylaxis after administration of the Comirnaty vaccine in New Zealand.²

It is essential that vaccinators administering COVID-19 vaccines can promptly identify and provide emergency treatment for anaphylaxis.

Anaphylaxis

Anaphylaxis is a severe, life-threatening, acute hypersensitivity reaction characterised by:

- rapidly evolving airway compromise due to pharyngeal or laryngeal oedema
- and/or wheeze and increased work of breathing due to bronchospasm
- and/or circulatory effects, such as hypotension and/or tachycardia.

Although not always seen, most cases are associated with skin and mucosal changes (eg, flushing, hives or welts, swelling of lips, face and eyes).³⁻⁶ People sometimes report perioral numbness/tingling as a first sign of anaphylaxis. It is very important to start treatment if anaphylaxis is suspected, even if these signs are not observed.

Anaphylaxis results from the sudden degranulation of mast cells and basophils, releasing mediators such as histamine, proteases, prostaglandins and leukotrienes into the circulation.^{7,8}

Risk factors for anaphylaxis to Comirnaty vaccine

Individuals should not receive the Comirnaty vaccine if they have a history of anaphylaxis to any of the ingredients in the vaccine.^{1,9,10} The vaccine ingredients are listed in the New Zealand [data sheet](#) (see section 2 for the active ingredient and section 6.1 for the list of excipients).⁹

Polyethylene glycol (PEG), also known as macrogol, is an ingredient in mRNA COVID-19 vaccines. PEG is present in many different types of medicines and is recognised as an allergen that can trigger anaphylaxis in some people.^{1,10-13}

Individuals with a history of an anaphylaxis-type reaction to any other substance have an increased risk of an anaphylactic response to mRNA COVID-19 vaccines.¹⁰ These individuals can still receive the vaccine but should be observed for a minimum of 30 minutes and be given clear advice on symptoms of anaphylaxis and how to call for help, before leaving the vaccination facility.¹⁰

Treatment of anaphylaxis

Adrenaline is the first-line treatment for anaphylaxis and should be given without delay as soon as anaphylaxis is suspected.^{6,14,15}

1:1000 adrenaline must always be readily available at vaccination centres.

Adrenaline should be administered by deep intramuscular injection into the outer thigh. Most adults should receive 0.5 mg as an initial dose (0.5 mL of **1:1000** adrenaline). If it is known or suspected that the individual weighs less than 50 kg, the dose can be reduced using 0.01 mL/kg of **1:1000** adrenaline up to a maximum of 0.5 mL per dose. The dose can be repeated every five minutes as required until definitive help arrives.¹⁴

All cases of anaphylaxis should be admitted to hospital for observation.^{6,14,15}

Tests to confirm anaphylaxis

Mast cell tryptase is a highly specific but insensitive marker for anaphylaxis.³ Tryptase levels are elevated from 15 minutes to 3 hours after the onset of anaphylaxis.^{16,17}

Blood samples taken up to 4–6 hours from onset may still show an elevated tryptase level.^{3,5} A further sample taken more than 24 hours after resolution of symptoms should be obtained as a baseline measure.

An acute serum tryptase level greater or equal to 2 µg/L + (1.2 x baseline level) supports the diagnosis of anaphylaxis.^{16,17}

Recording and reporting of anaphylaxis following Comirnaty vaccination

Following the immediate emergency management of the patient and arranging transfer to hospital, the anaphylaxis event should be documented in the COVID-19 Immunisation Register (CIR). Adverse events following immunisation (AEFIs) that occur after the person has left the vaccination centre should be reported to the Centre for Adverse Reactions Monitoring (CARM) **using the online form**. It is important to include as much detail as possible in the description of the suspected anaphylaxis event, including symptoms, signs, time of onset and response to treatment. Reports of suspected anaphylaxis will be assessed by CARM against the Brighton Collaboration case definition for anaphylaxis.¹⁸

Implications of anaphylaxis for further vaccination

Individuals who experience anaphylaxis to the first dose of Comirnaty should not receive further doses of the vaccine.^{1,9,10}

References

1. Australasian Society of Clinical Immunology and Allergy (ASCI). 2021. *Allergy, Immunodeficiency, Autoimmunity and COVID-19 Vaccination Position Statement*, 14 April 2021. URL: allergy.org.au/hp/papers/ascia-hp-position-statement-covid-19-vaccination (accessed 19 April 2021).
2. Medsafe. 2021. *Safety report #5 – 3 April 2021* published 5 May 2021. URL: medsafe.govt.nz/COVID-19/safety-report-5.asp (accessed 5 May 2021).
3. Safety Platform for Emergency vAccines (SPEAC). 2021. *S02- D2.5.2.1 – AESI Case Definition Companion Guide for 1st Tier AESI: Anaphylaxis*. URL: brightoncollaboration.us/wp-content/uploads/2021/03/SPEAC_D2.5.2.1_Anaphylaxis-Case-Definition-Companion-Guide_V1.0-12070-1.pdf (accessed 19 April 2021).
4. Rüggeberg JU, Gold MS, Bayas J-M, et al. 2007. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine* 25(31): 5675–84. DOI: <https://doi.org/10.1016/j.vaccine.2007.02.064> (accessed 19 April 2021).
5. National Institute for Health and Care Excellence (NICE). 2020. *Anaphylaxis: Assessment and referral after emergency treatment. Clinical guideline [CG134]*, 14 December 2011 (last updated 24 August 2020). URL: [nice.org.uk/guidance/cg134](https://www.nice.org.uk/guidance/cg134) (accessed 19 April 2021).

6. Australasian Society of Clinical Immunology and Allergy (ASCIA). 2020. *ASCIA Guidelines – Acute Management of Anaphylaxis*. URL: allergy.org.au/hp/papers/acute-management-of-anaphylaxis-guidelines (accessed 19 April 2021).
7. Kemp SF. 2019. Pathophysiology of anaphylaxis. In: *UpToDate* 31 October 2019. URL: uptodate.com/contents/pathophysiology-of-anaphylaxis (accessed 21 April 2021).
8. Castells MC and Phillips EJ. 2020. Maintaining safety with SARS-CoV-2 vaccines. *New England Journal of Medicine* 384(7): 643-9. DOI: 10.1056/NEJMra2035343 (accessed 21 April 2021).
9. Pfizer New Zealand Ltd. 2021. *Comirnaty COVID-19 vaccine New Zealand Data Sheet* 6 April 2021. URL: medsafe.govt.nz/profs/Datasheet/c/comirnatyinj.pdf (accessed 21 April 2021).
10. Immunisation Advisory Centre (IMAC). 2021. *COVID-19 vaccinator information* March 2021. URL: immune.org.nz/covid-19-vaccinator-information (accessed 19 April 2021).
11. Garvey LH and Nasser S. 2021. Anaphylaxis to the first COVID-19 vaccine: is polyethylene glycol (PEG) the culprit? *British Journal of Anaesthesia* 126(3): e106-8. DOI: <https://doi.org/10.1016/j.bja.2020.12.020> (accessed 19 April 2021).
12. Sellaturay P, Nasser S, Islam S, et al. 2021. Polyethylene glycol (PEG) is a cause of anaphylaxis to the Pfizer/BioNTech mRNA COVID-19 vaccine. *Clinical & Experimental Allergy* 00:1-3. DOI: <https://doi.org/10.1111/cea.13874> (accessed 20 April 2021).
13. Stone CA, Liu Y, Relling MV, et al. 2019. Immediate hypersensitivity to polyethylene glycols and polysorbates: more common than we have recognized. *The Journal of Allergy and Clinical Immunology: In Practice* 7(5): 1533-1540.e8. DOI: <https://doi.org/10.1016/j.jaip.2018.12.003> (accessed 20 April 2021).
14. New Zealand Resuscitation Council. 2019. *Anaphylaxis* January 2019. URL: nzrc.org.nz/assets/Uploads/ANZCOR-Anaphylaxis-2019.pdf (accessed 19 April 2021).
15. Ministry of Health. 2020. *Immunisation Handbook 2020: Anaphylaxis response/management* 25 September 2020. URL: health.govt.nz/our-work/immunisation-handbook-2020/anaphylaxis-response-management (accessed 19 April 2021).
16. Kelso JM. 2020. Anaphylaxis: confirming the diagnosis and determining the cause(s). In: *UpToDate* 28 July 2020. URL: uptodate.com/contents/anaphylaxis-confirming-the-diagnosis-and-determining-the-causes (accessed 21 April 2021).
17. Cardona V, Ansotegui IJ, Ebisawa M, et al. 2020. World Allergy Organization anaphylaxis guidance 2020. *World Allergy Organization Journal* 13(10): 100472. DOI: <https://doi.org/10.1016/j.waojou.2020.100472> (accessed 19 April 2021).
18. Brighton Collaboration. 2021. *Brighton Collaboration Case Definitions*. URL: brightoncollaboration.us/category/pubs-tools/case-definitions/ (accessed 19 April 2021).

MARC's remarks: March 2021 meeting

The Medicines Adverse Reactions Committee (MARC) convened via videoconference on 11 March 2021.

The Committee reviewed the risk of postpartum haemorrhage (PPH) with the use of **selective serotonin reuptake inhibitors (SSRIs)** and **serotonin-noradrenaline reuptake inhibitors (SNRIs)**. The Committee considered that the evidence supports a small increased risk of PPH when SSRIs or SNRIs are used in the month up to/close to delivery but emphasised that this risk needs to be balanced with the benefits of continuing treatment. The Committee recommended that Medsafe write to the sponsors of these medicines to add this risk to the data sheets. The Committee also recommended that this issue is highlighted in *Prescriber Update* (see the article on page 23) and communicated to the relevant professional bodies.

The Committee reviewed the requirements for frequency and duration of monitoring for agranulocytosis in patients taking **clozapine**. The Committee noted there is a lack of evidence by which the safety of different monitoring regimens can be compared, and that agranulocytosis is one concern among a number of safety issues related to clozapine. It was also noted that Māori are overrepresented in the population of patients taking clozapine. The Committee recommended further investigation and consultation with the sector on safe use of clozapine.

See the Medsafe website for the [MARC meeting minutes](#) and the [reports presented to the MARC](#).

WE NEED YOUR HELP!

Please send your reports to CARM for the potential safety issues* listed in the table below.

Medicine(s)	Potential safety issue	Active monitoring ends
Pregabalin	Possible risk of bullous dermatitis and exfoliating skin reactions	25 November 2021

- **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.

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

Prednisone treatment – follow dosing recommendations

Key messages

- Prednisone dosing should be individualised and in line with clinical guidelines for the patient's condition and disease severity.
- The patient must be given clear instructions about when and how to stop prednisone, including detailed instructions for dose tapering if required.

Background

The Health and Disability Commissioner (HDC) recently notified Medsafe of a case concerning a patient who experienced steroid withdrawal symptoms after taking high-dose prednisone for an infective exacerbation of asthma.¹ The patient told HDC that she was suffering from prednisone withdrawal symptoms, including shaking, sweats, fatigue, puffy face and swollen legs.¹

Dosing of prednisone

Prednisone dosing should be determined on case-by-case basis taking into consideration the condition being treated and its severity, the patient's weight and comorbidities, and interactions with other medicines.^{2,3} In general, prednisone should be used at the lowest effective dose and for the shortest duration. Local clinical guidelines should be consulted for the appropriate regimen for specific conditions.

Stopping prednisone

Prolonged use of prednisone can result in suppression of the hypothalamic-pituitary-adrenal axis. Abrupt cessation or a too-rapid withdrawal of prednisone may cause symptoms of adrenal insufficiency,⁴ such as abdominal pain, nausea, diarrhoea, weakness and hypotension.⁵

The need for gradual prednisone withdrawal should be assessed on a case-by-case basis. Generally, dose tapering is required for patients who have:⁴

- received more than 40 mg of prednisone per day for more than one week
- been given repeat prednisone doses in the evening

- received prednisone for more than 3 weeks
- have recently had repeated courses
- have taken a short course within one year of stopping long-term therapy
- have other possible causes of adrenal suppression.

During corticosteroid withdrawal the dose may be reduced rapidly down to physiological doses (equivalent to prednisolone 7.5 mg daily) and then reduced more slowly. Assessment of the condition being treated may be needed during withdrawal to ensure that relapse does not occur.⁴



It is important to provide clear written instructions to the patient about when and how to stop prednisone, including detailed instructions for dose tapering if required.

References

1. Health & Disability Commissioner. 2021. *Prescription error for woman with respiratory complaint*. URL: www.hdc.org.nz/decisions/search-decisions/2021/19hdc01826/ (accessed 16 April 2021).
2. UpToDate. *Prednisone: drug information* Topic 9809 version 480.0. URL: uptodate.com/contents/prednisone-drug-information (accessed 16 April 2021).
3. Asthma and Respiratory Foundation NZ. 2020. *NZ Adolescent & Adult Asthma Guidelines 2020*. URL: nzrespiratoryguidelines.co.nz/uploads/8/3/0/1/83014052/arfnz_adolescent_and_adult_asthma_guidelines_.pdf (accessed 25 March 2021).
4. New Zealand Formulary (NZF). 2021. *NZF v107: Cautions and contra-indications of corticosteroids* 1 May 2021. URL: nzf.org.nz/nzf_3812 (accessed 5 May 2021).
5. Nieman, LK. 2018. Clinical manifestations of adrenal insufficiency in adults. In: *UpToDate* 26 October 2018. URL: uptodate.com/contents/clinical-manifestations-of-adrenal-insufficiency-in-adults (accessed 5 May 2021).

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](#).

Date	Communication	Topic
31/05/2021	Monitoring	 Possible risk of bullous dermatitis and exfoliating skin reactions with pregabalin
17/05/2021	Dear Healthcare Professional Letter	Supply of Engerix-B paediatric vaccine – Australian pack (PDF, 2 pages, 209 KB)
17/05/2021	Dear Healthcare Professional Letter	Novatretrin (acitretin) – increase in period during which effective contraception must be used, and information about blood donations (PDF, 2 pages, 598 KB)
29/04/2021	Notices	Unapproved COVID-19 vaccines – restriction on importation, manufacture, supply and use
29/04/2021	Alert	Fluad Quad – a newly funded influenza vaccine for people aged 65 years and older
27/04/2021	Monitoring	COVID-19 vaccines and rare cases of blood clots with bleeding: no current risk with Comirnaty (Pfizer/ BioNTech) vaccine
13/04/2021	Dear Healthcare Professional Letter	Important information: Influenza vaccines for SH2021 (PDF, 2 pages, 259 KB)
07/04/2021	Monitoring	 UPDATE: Possible risk of psoriasis exacerbation with bupropion

28/03/2021	Dear Healthcare Professional Letter	Macrobid modified-release capsule release characteristics and in-use shelf life (PDF, 2 pages, 242 KB)
23/03/2021	Dear Healthcare Professional Letter	Priorix vaccine will be supplied as a single-dose in a Singapore pack (PDF, 2 pages, 319 KB)
23/03/2021	Monitoring	UPDATE: Concern reported with the use of NovoRapid®Penfill® (insulin aspart; 3 mL cartridge) by type 1 diabetes patients
16/03/2021	Alert	UPDATE – Rocuronium bromide solution for injection 10mg/mL, Hameln, and reports of lack of efficacy
15/03/2021	Dear Healthcare Professional Letter	Clopine 50 mg/mL oral suspension brand is being replaced by Versacloz 50 mg/mL oral suspension (PDF, 1 page, 177 KB)
02/03/2021	Alert	UPDATE – Yes! Cassette Pregnancy Test Kit (also known as Smiths BioMed Rapid Pregnancy Test Kit) – Reports of false positives presenting as faint lines and inconclusive results

Small increased risk of postpartum haemorrhage with use of serotonergic antidepressants close to delivery

Key messages

- Observational studies have shown a small increased risk of postpartum haemorrhage when selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs) are used during the month up to delivery.
- Healthcare professionals should continue to consider the benefits of treating depression for the mother with this new, small risk of postpartum bleeding.

At their 185th meeting in March 2021, the Medicines Adverse Reactions Committee (MARC) reviewed the risk of postpartum haemorrhage when SSRIs (citalopram, escitalopram, fluoxetine, sertraline and paroxetine) and SNRIs (venlafaxine) are used during the month up to delivery.

The MARC considered that an increased risk of postpartum haemorrhage was biologically plausible, as serotonin plays a role in platelet function.¹

Observational studies have shown a small increased risk of postpartum haemorrhage (less than a two-fold increase) when SSRIs and SNRIs were used in the month up to delivery. The risk may also apply to vortioxetine, a newer antidepressant.^{2,3}

The increase in absolute risk of postpartum haemorrhage was considered to be small. One observational study estimated there may be about one excess case of postpartum haemorrhage for every 80 to 100 women taking these antidepressants close to the time of delivery.⁴

A 2015 systematic review noted that information on the exact amount of blood loss and the clinical and therapeutic consequences of the blood loss (such as transfusion and prolonged hospital stay) was not available in any of the studies included in the review.⁵

In the context of the above information, healthcare professionals are reminded to continue to consider the benefits of treating depression for the mother with this new, small risk of postpartum bleeding.²

The MARC recommended that all data sheets for SSRIs, SNRIs and vortioxetine be updated,⁶ and Medsafe is working with the sponsors to do this.

References

1. Hirsch M, Birnbaum RJ. 2020. Selective serotonin reuptake inhibitors: pharmacology, administration, and side effects. In: *UpToDate* 16 March 2020. URL: [uptodate.com/contents/selective-serotonin-reuptake-inhibitors-pharmacology-administration-and-side-effects](https://www.uptodate.com/contents/selective-serotonin-reuptake-inhibitors-pharmacology-administration-and-side-effects) (accessed 16 March 2021).
2. Medicines and Healthcare products Regulatory Agency. 2021. SSRI/SNRI antidepressant medicines: small increased risk of postpartum haemorrhage when used in the month before delivery. *Drug Safety Update* 14(6): 5. URL: [gov.uk/drug-safety-update/ssri-slash-snri-antidepressant-medicines-small-increased-risk-of-postpartum-haemorrhage-when-used-in-the-month-before-delivery](https://www.gov.uk/drug-safety-update/ssri-slash-snri-antidepressant-medicines-small-increased-risk-of-postpartum-haemorrhage-when-used-in-the-month-before-delivery) (accessed 8 April 2021).
3. European Medicines Agency. 2020. *PRAC recommendations on signals* 26 October 2020. URL: [ema.europa.eu/en/documents/prac-recommendation/prac-recommendations-signals-adopted-28-september-1-october-2020-prac-meeting_en.pdf](https://www.ema.europa.eu/en/documents/prac-recommendation/prac-recommendations-signals-adopted-28-september-1-october-2020-prac-meeting_en.pdf) (accessed 8 April 2021).
4. Palmsten K, Hernández-Díaz S, Huybrechts KF, et al. 2013. Use of antidepressants near delivery and risk of postpartum hemorrhage: cohort study of low income women in the United States. *British Medical Journal* 21(347): DOI: 10.1136/bmj.f4877 (accessed 12 February 2021).
5. Bruning AHL, Heller HM, Kieviet N, et al. 2015. Antidepressants during pregnancy and postpartum hemorrhage: a systematic review. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 189: 38-47. DOI: 10.1016/j.ejogrb.2015.03.022 (accessed 12 February 2021).
6. Medsafe. 2021. *Minutes of the 185th Medicines Adverse Reactions Committee meeting 11 March 2021*. URL: [medsafe.govt.nz/profs/adverse/Minutes185.htm](https://www.medsafe.govt.nz/profs/adverse/Minutes185.htm) (accessed 5 May 2021).

Gathering knowledge from adverse reaction reports: June 2021

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,b}	Reaction description and data sheet information ^{b,c}
CARM ID: 138728 Age: 81 Gender: Male Medicine(s): Adalimumab Reaction(s): Colon cancer, metastasis	<p>A patient administered adalimumab developed colon cancer and passed away four months after diagnosis.</p> <p>The Humira data sheet states that it is not known if adalimumab treatment influences the risk for developing dysplasia or colon cancer. All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma, or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course.</p>
CARM ID: 138899 Age: 50 Gender: Male Medicine(s): Warfarin Reaction(s): Calcinosi (calciophylaxis)	<p>A patient developed calciophylaxis a year after starting warfarin treatment. The patient had pre-existing renal disease and was on haemodialysis.</p> <p>Calciophylaxis is described in the Coumadin and Marevan data sheets as a rare syndrome of vascular calcification with cutaneous necrosis, associated with high mortality. The condition is mainly observed in patients with end-stage renal disease on dialysis. Rare cases of calciophylaxis have been reported in patients receiving warfarin, also in the absence of renal disease.</p> <p>See also the September 2017 <i>Prescriber Update</i> article, Warfarin and calciophylaxis – a rare but serious adverse event.</p>

<p>CARM ID: 139011 Age: Neonate Gender: Male Medicine(s): Paracetamol Reaction(s): Hepatic enzymes increased, coagulation disorder, thyroid disorder, INR increased, hyperbilirubinaemia</p>	<p>A preterm neonate was administered oral and intravenous paracetamol. He developed acute onset liver failure with coagulation derangement and hyperbilirubinaemia, as well as deranged thyroid function, despite acetylcysteine administration. No other cause for the events was found.</p> <p>The Paracetamol Kabi data sheet states that there is a risk of poisoning, particularly in young children. Unintentional overdose can lead to serious liver damage and death. It is essential to follow both the weight-related dose recommendations and to consider individual patient risk factors for hepatotoxicity. See also the September 2019 <i>Prescriber Update</i> article, Paracetamol – Dangerous when not used correctly.</p>
<p>CARM ID: 139143 Age: 14 Gender: Female Medicine(s): Minocycline Reaction(s): Intracranial pressure increased</p>	<p>After taking minocycline for several months, the patient experienced constant frontal headache, tinnitus, visual disturbances and pain around both eyes. The patient had raised opening pressure at lumbar puncture, and an MRI revealed changes to the optic nerve, consistent with intracranial hypertension.</p> <p>The Minomycin data sheet states that pseudotumour cerebri (idiopathic intracranial hypertension) in adults has been associated with the use of tetracyclines including minocycline. The usual clinical manifestations are headache and blurred vision.</p> <p>See also the March 2016 <i>Prescriber Update</i> article, Idiopathic intracranial hypertension.</p>
<p>CARM ID: 139293 Age: 57 Gender: Female Medicine(s): Tacrolimus Reaction(s): Leukoencephalopathy, drug level increased</p>	<p>The patient presented to hospital with worsening co-ordination and gait instability. Tacrolimus levels were increased. MRI results were consistent with posterior reversible encephalopathy syndrome (PRES; also known as reversible posterior leukoencephalopathy syndrome). The patient was started on antihypertensives and tacrolimus withdrawn. Recovery took several months.</p> <p>The Tacrolimus Sandoz data sheet states that PRES has been reported in patients treated with tacrolimus. If patients taking tacrolimus present with symptoms indicating PRES, such as headache, altered mental status, seizures, and visual disturbances, a radiological procedure (eg, MRI) should be performed. If PRES is diagnosed, adequate blood pressure and seizure control and immediate discontinuation of systemic tacrolimus is advised. Most patients completely recover after appropriate measures are taken.</p> <p>See also the March 2017 <i>Prescriber Update</i> article, Posterior reversible (leuko) encephalopathy syndrome (PRES) – increasingly linked to medicines.</p>
<p>CARM ID: 139818 Age: 73 Gender: Male Medicine(s): Atorvastatin Reaction(s): Gynaecomastia, nipple pain</p>	<p>After his atorvastatin dose was increased, the patient developed lumps of breast tissue under the nipples and nipple sensitivity.</p> <p>The Lorstat data sheet includes gynaecomastia as a postmarketing adverse event.</p>

CARM ID: 139669 Age: 45 Gender: Female Medicine(s): Imiquimod Reaction(s): Application site infection, application site oedema, application site pain	Following treatment to the vaginal area with imiquimod cream, the patient developed an application site infection, severe swelling and pain.
	The Imiquimod Cream and APO-Imiquimod data sheets state that care should be taken if applying imiquimod at the opening of the vagina, as local skin reactions (including erythema, erosion, oedema, vesicles, scabbing, desquamation/flaking and induration) on mucosal surfaces can result in pain or swelling. Infections and application site disorders are also listed adverse reactions.

Notes:

- Only the medicines suspected to have caused the reaction are listed in the table.
- The reactions listed in the 'Case details' column are coded according to the Medical Dictionary for Regulatory Activities (MedDRA), an internationally used set of standardised terms relating to medical conditions, medicines and medical devices. The reactions listed in the 'Reaction description' column are based on what was reported to CARM, and do not always match the MedDRA term.
- 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 \(SMARS\)](#).

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).

Nitrofurantoin: prescribe by brand

Key messages

- Nitrofurantoin is available as immediate-release tablets (Nifuran), and more recently, as modified-release capsules (Macrobid).
- To minimise confusion between formulations, healthcare professionals are reminded to prescribe nitrofurantoin by brand.

Nitrofurantoin is an antibiotic indicated for the treatment or prophylaxis of urinary tract infection.¹

Nitrofurantoin is available as immediate-release tablets (Nifuran),² and more recently, as modified-release capsules (Macrobid).³ Healthcare professionals should note that the Macrobid product packaging does not state that:

- the capsule is modified release
- it currently has a 90 day 'in-use' shelf life.

Further information about Macrobid is available in the [Dear Healthcare Professional Letter](#) (PDF, 2 pages, 242 KB).

Healthcare professionals are reminded to prescribe nitrofurantoin by brand, because:

- the two formulations have different dosing regimens, which could potentially result in over- or under-dosing⁴
- Macrobid is not indicated for long-term prophylaxis or for children aged under 12 years.³

References

1. Medsafe. 2020. Spotlight on nitrofurantoin. *Prescriber Update* 41(1): 2–4.
URL: medsafe.govt.nz/profs/PUArticles/March2020/Spotlight-nitrofurantoin.html (accessed 29 March 2021).
2. WM Bamford & Company Limited. 2017. *Nifuran New Zealand Data Sheet* 10 July 2017.
URL: medsafe.govt.nz/profs/Datasheet/n/Nifurantab.pdf (accessed 26 March 2021).
3. Te Arai BioFarma Limited. 2021. *Macrobid New Zealand Data Sheet* 14 February 2021.
URL: medsafe.govt.nz/profs/Datasheet/m/macrobidcap.pdf (accessed 26 March 2021).
4. New Zealand Formulary (NZF). 2021. *NZF v105: Nitrofurantoin* 1 March 2021.
URL: nzf.org.nz/nzf_3293 (accessed 26 March 2021).

The paradox of opioid-induced hyperalgesia

Key messages

- Opioid-induced hyperalgesia (OIH) is a paradoxical condition whereby long-term opioid use induces or sensitise patients to acute pain.
- OIH may present as either increased clinical pain, diffuse allodynia not associated with the original pain, or both, which worsen in response to increasing the opioid dose.
- If OIH is suspected, re-evaluation of the patient's pain management may be required.

Opioids are generally indicated for treatment of moderate to severe acute pain and for cancer pain. They are not recommended for chronic non-cancer pain due to concerns over the long-term efficacy and safety of treatment, including the risk of abuse, misuse and dependence.^{1,2}

Multiple adverse events are associated with long-term opioid therapy, including opioid-induced hyperalgesia.² At a recent Medicines Adverse Reactions Committee meeting, the Committee recommended highlighting this condition to prescribers.³

Opioid-induced hyperalgesia (OIH)

Long-term use of opioids can paradoxically induce or sensitise patients to acute pain, a condition called 'opioid-induced hyperalgesia' (OIH).² The type of pain experienced might be the same as or different from the original underlying pain,² and in some cases, patients may experience pain from ordinarily non-painful stimuli (allodynia).⁴ The development of OIH may explain the loss of treatment efficacy in some patients.²

In preclinical laboratory settings, OIH is a well-established, easily reproducible state of nociceptive sensitisation caused by exposure to opioids.⁴ However, there is limited evidence for the existence^{1,2} of OIH in patients with chronic non-cancer or cancer-related pain.⁵ A recent systematic review concluded that OIH was evident in patients after chronic opioid exposure, but that the findings were dependent on both the pain stimulus and assessment measures.⁶

OIH is not opioid tolerance

Opioid tolerance is characterised by decreasing efficacy of the opioid, which can be overcome by increasing the dose.^{2,5} Pain is usually limited to its original site and improves in response to opioid dose escalation.⁵ In contrast, OIH refers to reduced pain tolerance.

OIH may present as either increased clinical pain, diffuse allodynia not associated with the original pain, or both, which worsen in response to increasing the opioid dose.^{2,5}

Management

Suspect OIH when an opioid treatment's effect seems to wane in the absence of disease progression or the patient experiences increased levels of pain with increasing opioid dosages.² The patient may also report unexplained pain or diffuse allodynia not associated with the original pain.²

Re-evaluate pain management strategies if OIH is suspected. This may include non-pharmacological pain treatment, patient education, reducing the opioid dose or changing to a different opioid.⁴ Follow local guidelines, including referral to a pain specialist team where available.¹

References

1. New Zealand Formulary (NZF). 2021. *NZF v106: Opioid analgesics* 1 April 2021. URL: nzf.org.nz/nzf_2456 (accessed 12 April 2021).
2. Lee M, Silverman S, Hansen H, et al. 2011. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician* 14(2): 145-61. URL: painphysicianjournal.com/current/pdf?article=MTQ0Ng%3D%3D&journal=60 (accessed 12 April 2021).
3. Medsafe. 2020. *Minutes of the 184th Medicines Adverse Reactions Committee Meeting 3 December 2020*. URL: medsafe.govt.nz/profs/adverse/Minutes184.htm (accessed 12 May 2021).
4. Portenoy R, Mehta A and Ahmed E. 2021. Prevention and management of side effects in patients receiving opioids for chronic pain. In: *UpToDate* 6 January 2021. URL: uptodate.com/contents/prevention-and-management-of-side-effects-in-patients-receiving-opioids-for-chronic-pain (accessed 12 April 2021).
5. Eisenberg E, Suzan E and Pud D. 2015. Opioid-induced hyperalgesia (OIH): a real clinical problem or just an experimental phenomenon? *Journal of Pain and Symptom Management* 49(3): 632-6. DOI: <https://doi.org/10.1016/j.jpainsymman.2014.07.005> (accessed 12 April 2021).
6. Higgins C, Smith B and Matthews K. 2019. Evidence of opioid-induced hyperalgesia in clinical populations after chronic opioid exposure: a systematic review and meta-analysis. *British Journal of Anaesthesia* 122(6): e114-26. DOI: <https://doi.org/10.1016/j.bja.2018.09.019> (accessed 7 April 2021).

Recent approvals: new active ingredients or new indications

For the period 16 January 2021 to 15 April 2021.

Recent approvals of medicines with new active ingredients

Trade name (active ingredient)	Dose form and strength(s)	Therapeutic area
Comirnaty (COVID-19 mRNA vaccine)	Concentrate for injection 0.5 mg/mL	Immunisation to prevent COVID-19
Mayzent (siponimod)	Film coated tablet 0.25 mg 2 mg	Multiple sclerosis
Vyvanse (lisdexamfetamine)	Capsule 30 mg 50 mg 70 mg	Attention deficit hyperactivity disorder (ADHD)

Approved medicines with new indications

Trade Name (active ingredient)	Dose form and strength(s)	New therapeutic area(s)
Forxiga (dapagliflozin)	Film coated tablet 10 mg	Chronic kidney disease
Opdivo (nivolumab)	Concentrate for infusion 40 mg/4 mL 100 mg/10 mL	Non-small cell lung cancer
Sirturo (bedaquiline)	Tablet 100 mg	Tuberculosis in paediatric patients (aged 12 years to less than 18 years)
Sprycel (dasatinib)	Film coated tablet 20 mg 50 mg 70 mg 100 mg	Paediatric patients with Philadelphia chromosome positive: <ul style="list-style-type: none">• chronic myeloid leukaemia• acute lymphoblastic leukaemia
Toujeo (neutral insulin)	Solution for injection 300 IU/mL	Diabetes mellitus in patients aged 6 years and older

See the Medsafe website for:

- [more information about these medicines](#)
- [data sheets of currently marketed medicines](#).

Medsafe

New Zealand Medicines and Medical Devices Safety Authority

A business unit of the Ministry of Health

Editor

Vikki Cheer

Medsafe, PO Box 5013, Wellington 6140, New Zealand

Ph: (04) 819 6800

Email: medsafeadrquery@health.govt.nz

Editorial Team

Andrea Kerridge, Senior Advisor Pharmacovigilance

Dr Geraldine Hill, Senior Medical Advisor

Maria Storey, Senior Advisor Pharmacovigilance

Nevin Zhong, Advisor Pharmacovigilance

Dr Susan Kenyon, PhD, Manager Clinical Risk

Tegan Coventry, Advisor Pharmacovigilance

Acknowledgements

Dr Adam Pomerleau, National Poisons Centre

Dr Enver Yousuf, Capital and Coast District Health Board

Dr Michael Tatley, Centre for Adverse Reactions Monitoring

Medsafe also acknowledges the contribution of the New Zealand Pharmacovigilance Centre in providing data and analysis for articles.

Clinical Advisor Dr Tina Ireland

Group Manager Chris James

Prescriber Update is published and distributed by Medsafe in the interests of safer, more effective use of medicines and medical devices. While the information and advice included in this publication are believed to be correct, no liability is accepted for any incorrect statement or advice. No person proposing to prescribe a medicine to any other person should rely on the advice given in this publication without first exercising his or her professional judgement as to the appropriateness of administering that medicine to another person.

Prescriber Update is available at
medsafe.govt.nz/publications/prescriber-update.asp

Data sheets, consumer medicine information, media releases, medicine classification issues and adverse reaction forms are available at medsafe.govt.nz

Published with the permission of the Director-General of Health.



This work is licensed under the Creative Commons Attribution 4.0 International licence. In essence, you are free to: share, ie, copy and redistribute the material in any medium or format; adapt, ie, remix, transform and build upon the material. You must give appropriate credit, provide a link to the licence and indicate if changes were made.



[New Zealand Government](https://www.govt.nz/)

