Prescriber Update

Vol. 40 No. 3 September 2019

www.medsafe.govt.nz ISSN 1179-075X (online)

Contents

MEDSAFE
NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY
A BUSINESS UNIT OF THE MINISTRY OF HEALTH
www.medsafe.govt.nz

MINISTRY OF HEALTH
MANATŪ HAUORA

New Zealand Government

Spotlight on vildagliptin

Key messages

- Vildagliptin is indicated as monotherapy or in combination therapy for the treatment of type 2 diabetes mellitus.
- Vildagliptin is a potent and selective dipeptidyl-peptidase-4 inhibitor that improves glycaemic control by enhancing the sensitivity of pancreatic beta cells to glucose, resulting in improved glucose-dependent insulin secretion.
- Hepatotoxicity is the most significant risk of harm. Perform liver function tests before starting treatment with vildagliptin, at 3-monthly intervals during the first year of treatment, and periodically thereafter.

Vildagliptin (Galvus) was approved by Medsafe in October 2008. The combination product vildagliptin + metformin (Galvumet) was approved in May 2009. PHARMAC funded both of these medicines in October 2018.

What is vildagliptin?

Vildagliptin is a potent and selective dipeptidyl-peptidase-4 (DPP-4) inhibitor approved for the treatment of type 2 diabetes as an adjunct to diet and exercise[1–3].

In New Zealand, vildagliptin tablets can be used as monotherapy or in dual or triple combination treatment with other antidiabetic agents[2].

See the medicine data sheet for full prescribing information (the website URLs are listed below).

Considerations for use

Hepatotoxicity is the most significant risk of harm. Perform liver function tests before starting treatment, at 3-monthly intervals during the first year of treatment, and periodically thereafter[2,3]. Stopping treatment in the event of a persistent increase in AST or ALT results in a return to normal levels.

Avoid using vildagliptin during pregnancy unless the expected benefits outweigh any potential risks[2,3].

Galvumet (vildagliptin + metformin) is contraindicated in patients with severe renal impairment, congestive heart failure and metabolic acidosis[3].

Interactions

Vildagliptin is not metabolised by the cytochrome P 450 enzymes and has a low potential for drug-drug interactions.[2,3] However, interactions with metformin should be checked when using the combination product Galvumet. Refer to the medicine data sheet for further information regarding interactions.

Adverse drug reactions

The most common adverse reactions identified from clinical trials were dizziness, headache, constipation and peripheral oedema[2].

As of 30 June 2019, the Centre for Adverse Reactions Monitoring (CARM) had received 15 reports where vildagliptin (alone or in combination with metformin) was the suspect medicine. These 15 reports describe 36 reactions, including hepatic reactions, oedema, cardiac disorders, mood disorders and gastrointestinal disorders.

Two reports described hepatic reactions:

- liver failure was reported in a patient with multiple co-morbidities (CARM ID: 130633)
- raised LFTs (liver function tests) were reported in another patient (CARM ID: 131133).

More information

See the medicine data sheet for full prescribing information, available on the Medsafe website.

- Galvus – **www.medsafe.govt.nz/profs/datasheet/g/galvustab.pdf**
- Galvumet – **www.medsafe.govt.nz/profs/datasheet/g/galvusmettab.pdf**.

See also 'Vildagliptin: a new treatment for type 2 diabetes', available on the bpac website (bpac.org.nz/2018/docs/vildagliptin.pdf).

References

1. bpac^{NZ}. 2018. *Vildagliptin: a new treatment for type 2 diabetes*. URL: https://bpac.org.nz/2018/docs/vildagliptin.pdf (accessed 25 June 2019).
2. Novartis New Zealand Limited. 2017. *Galvus New Zealand Data Sheet* January 2017. URL: www.medsafe.govt.nz/profs/Datasheet/g/galvustab.pdf (accessed 24 June 2019).
3. Novartis New Zealand Limited. 2018. Galvumet New Zealand Data Sheet August 2018. URL: www.medsafe.govt.nz/profs/Datasheet/g/galvusmettab.pdf (accessed 25 June 2019).

Paracetamol – Dangerous when not used correctly

Key messages

- Serious cases describing paediatric paracetamol dosing-related adverse events, including acute liver failure, have been reported in New Zealand. Medication errors associated with prescribing, dispensing and communication to caregivers were implicated in the reports.
- A list of actions for healthcare professionals to take when prescribing and dispensing paracetamol liquid for children is provided in Table 1 of this article.
- Medsafe will seek feedback on proposed changes to the Label Statements Database (LSD) for paracetamol in the coming weeks. Have your say by participating in the consultation, available at: **www.medsafe.govt.nz/consultations/current.asp**

In December 2018, the Medicines Adverse Reactions Committee (MARC) discussed a report of acute hepatic failure in a child given a suspected paracetamol overdose[1].

The Committee considered that this important event required further discussion and that a holistic response across different healthcare agencies was needed. At the MARC's request, a number of organisations met to discuss cases of paediatric paracetamol dosing-related adverse events reported in New Zealand.

Review of the New Zealand cases did not clearly implicate use of non-prescription paracetamol, although the source was not clear in some cases. However, medication errors associated with prescribing, dispensing and communication to caregivers were reported.

For example, one case report described a young child who was prescribed an excessive dose of paracetamol (34.5 mg/kg/dose). As a result, the child developed acute liver failure. Another case report described a young child who was inappropriately dosed with a ***table***spoon. The child also developed acute liver failure from the overdose.

Following review of the cases, the group recommended that healthcare professionals could take a number of actions to avoid these errors. These actions are summarised in Table 1.

Table 1: Actions to take when prescribing and dispensing paracetamol liquid for children

Only recommend paracetamol for an appropriate condition
Only use paracetamol for approved indications (ie, pain and/or fever).
Calculate the correct dose[a]
Use weight-based dosing.
Use actual body weight, not ideal body weight.
Never exceed the recommended adult dose.
Prescribe precisely
Specify the dose, the concentration of paracetamol liquid to be dispensed (ie, 120 mg/5mL or 250 mg/5mL), the mL volume to be administered and the maximum daily dose on the prescription. Including the child's current weight on the prescription can provide a valuable cross check at dispensing.
Dispense diligently
Check that the prescribed dose is appropriate/safe, that the correct strength of paracetamol liquid (120 mg/5mL or 250 mg/5mL) has been selected for dispensing and ensure that the dosing instructions are clearly written on the medicine label.
Ensure that the caregiver has access to an appropriate measuring device, suitable to administer the dose prescribed, and that they know how to measure the correct dose.
Check to see if the caregiver requires additional written information eg, **Paracetamol for babies and children**[b]
Communicate to the caregiver
Warn the caregiver that there are potential hazards associated with the use of paracetamol in children.
Ensure that the caregiver knows the dosing interval and the maximum number of doses per day.
Ensure that for families with more than one child, the caregiver is aware of the different doses required for each child and that there are two different strengths of paracetamol liquid available (120 mg/5mL and 250 mg/5mL).
Advise the caregiver to seek medical advice if they are unsure about the dose or if they think they have made a mistake.
Advise the caregiver to keep all medicine, including paracetamol liquid, out of reach and sight of children.
Advise the caregiver to shake the bottle before administering paracetamol liquid.

Notes

a. See the paracetamol dosing regimen in the New Zealand Formulary for Children, available at: https://www.nzfchildren.org.nz/nzf_2439

b. Health Navigator + PHARMAC. 2018. *Paracetamol for babies and children*. URL: www.healthnavigator.org.nz/media/5078/paracetamol-safe-use-of-paracetamol-for-children-july-2018.pdf

Medsafe has also reviewed the package labelling of over-the-counter (OTC) paracetamol liquid products. We will be seeking feedback on proposed changes to the Label Statements Database (LSD) for paracetamol in the coming weeks. Have your say by participating in the consultation, available at: **www.medsafe.govt.nz/consultations/current.asp**

References

1. Medsafe. 2018. *Minutes of the 176th Medicines Adverse Reaction Committee Meeting*. URL: www.medsafe.govt.nz/profs/adverse/Minutes176.htm (accessed 24 July 2019).

Stop and think before using botulinum toxin

Key Messages

- Products of botulinum are not interchangeable.
- The strength displayed in units is unique to each product and is not comparable across the different products.

Introduction

Botulinum toxin type A is a muscle relaxant used to treat a variety of disorders characterised by overactive muscle movement or muscle spasm. There are three products containing botulinum toxin type A approved in New Zealand (Table 1).

Table 1: Approved products containing botulinum toxin type A

Product	Botulinum toxin type A formulation	Botulinum toxin type A strength per vial	Funded
Botox	Complex of toxin and accessory proteins	100 U and 200 U	Yes
Dysport	Toxin-haemagglutinin complex	300 ipsen units and 500 ipsen units	Yes
Xeomin	Purified toxin only	50 U and 100 U	No

Botulinum toxin products are not interchangeable

There is a risk of medication error when botulinum toxin type A is prescribed, dispensed or administered. Unit doses of botulinum toxin type A are not therapeutically equivalent across products and these products are not interchangeable (see Table 1). The formulation of botulinum toxin type A in each product is different. In addition, the potency units are specific to the preparation and assay method used in the respective product. Please refer to the data sheets for full prescribing information and instructions for reconstitution[1–3].

References

1. Allergan (New Zealand) Limited. 2017. *Botox New Zealand Data Sheet* November 2017. URL: www.medsafe.govt.nz/profs/datasheet/b/Botoxinj.pdf (accessed 18 June 2019).
2. Healthcare Logistics. 2018. *Dysport New Zealand Data Sheet* 13 December 2018. URL: www.medsafe.govt.nz/profs/datasheet/d/Dysportinj.pdf (accessed 18 June 2019).
3. Healthcare Logistics. 2019. *Xeomin New Zealand Data Sheet* 17 January 2019. www.medsafe.govt.nz/profs/datasheet/x/Xeomininj.pdf (accessed 20 June 2019).

Fentanyl Sandoz: Patch placement

The Fentanyl Sandoz data sheet has been updated to include information about patch placement in young children and persons with cognitive impairment.

The upper back is the preferred location in these patients to minimise the potential of inappropriate patch removal.

The data sheet is available on the Medsafe website (**www.medsafe.govt.nz/profs/datasheet/f/fentanylsandozpatch.pdf**).

Medsafe Files – Episode 11: Communicating medicines information

Key Messages

- Medsafe provides information on the benefits and risks of harm of medicines so that you and your patients can make informed decisions about the use of medicines.
- Visit the Medsafe website to find information on approved medicines: **www.medsafe.govt.nz**
- You can subscribe to receive *Prescriber Update*, safety communications and regulatory updates.

An important part of Medsafe's role as regulator of therapeutic products is to provide medicines information to healthcare professionals, consumers and the pharmaceutical industry. The Medsafe website (**www.medsafe.govt.nz**) plays a crucial part in ensuring that everyone can access this information.

We recently updated the design of the Medsafe website, and we hope you enjoy using it. You can still access the same information as before, including:

- data sheets and consumer medicine information
- Medsafe safety communications
- *Prescriber Update*.

These resources are described in more detail below, along with how to stay informed.

Data sheets and consumer medicine information (CMI)

Information on the known benefits and risks of medicines is provided in data sheets for healthcare professionals and consumer medicine information (CMI) for patients.

You can search for data sheets and CMI here:
www.medsafe.govt.nz/Medicines/infoSearch.asp

Pharmaceutical companies are responsible for the content of data sheets and CMI, including keeping the information up-to-date. Medsafe provides guidelines for pharmaceutical companies to follow and can request data sheet updates as new information becomes available.

Please contact the pharmaceutical company named as the sponsor in the data sheet or CMI if you have any questions about the information in these documents.

Data sheets

Data sheets are written for healthcare professionals and can help during discussions with patients about whether a medicine is appropriate for them. Data sheets must now follow a set format – the information is in the same order in all data sheets, with clinical information near the beginning.

Prescription medicines and pharmacist-only (restricted) medicines must have a data sheet. Data sheets are optional for pharmacy-only medicines and general sales medicines.

Consumer medicine information (CMI)

CMI is an interpretation of the data sheet, written for patients. It contains advice such as what the medicine is used for, how to take it, what side effects can occur, and what to do if a dose is missed.

CMI is not intended to reduce or replace advice from healthcare professionals.

Although there is no legal requirement for CMIs, Medsafe encourages pharmaceutical companies to provide CMIs for their products.

Medsafe safety communications

Medsafe uses safety communications to communicate important new safety information for medicines and devices.

There are two types of Medsafe safety communications: monitoring and alerts.

Monitoring communications

Monitoring communications provide information on *newly identified potential safety concerns that are under review* by Medsafe.

Monitoring communications may be used to seek further adverse reaction reports under the Medicines Monitoring scheme. These communications display this symbol: 

No actions are generally recommended in monitoring communications, other than to follow the instructions provided with the medicine.

Alert communications

In contrast to monitoring communications, alerts are issued once Medsafe has *completed a review of the safety concern*.

Alert communications contain more information on the safety concern than monitoring communications and include specific advice on actions that healthcare professionals and consumers may need to take.

For further information on Medsafe safety communications, including communications issued in the last 12 months, visit: **www.medsafe.govt.nz/safety/SafetyCommunications.asp**

Prescriber Update

Prescriber Update is written for healthcare professionals to provide information on safety concerns with medicines and medical devices. It is published electronically four times a year.

Stay informed

You can subscribe to receive Prescriber Update and Medsafe safety communications at: **www.medsafe.govt.nz/profs/subscribe.asp**

You can also subscribe to receive weekly emails for new additions to the Medsafe website. These emails outline new and updated data sheets and CMI, plus other regulatory changes. Subscribe at: **www.medsafe.govt.nz/regulatory/subscribe.asp**

Direct-acting oral anticoagulants may not be the best choice for patients with antiphospholipid syndrome

Key Messages

- An increased rate of recurrent thrombotic events has been noted in patients with antiphospholipid syndrome (APS) treated with rivaroxaban compared to those treated with warfarin.
- APS patients who are triple positive (for lupus anticoagulant, anticardiolipin and anti-beta-2 glycoprotein I antibodies) are at the greatest risk of treatment failure.
- Other direct-acting oral anticoagulants may also be less effective than warfarin in patients with APS.
- Consider switching patients with APS requiring anticoagulant therapy to other therapy, such as warfarin.

In a recently-published study investigating anticoagulant treatment in patients with antiphospholipid syndrome (APS), warfarin was significantly more effective at preventing recurrent thromboembolic events than rivaroxaban (Xarelto)[1].

APS patients included in the trial were at high risk for thromboembolic events (triple positive for lupus anticoagulant, anticardiolipin and anti-beta-2 glycoprotein I antibodies).

The trial was terminated prematurely due to an excess of thromboembolic events among patients taking rivaroxaban. Thromboembolic events occurred in 7 (12%) of patients taking rivaroxaban compared to no thromboembolic events in patients randomised to warfarin.

Major bleeding occurred in 4 patients (7%) in the rivaroxaban group and 2 patients (3%) in the warfarin group.

There are no completed similar trials for the other direct-acting oral anticoagulants (DOACs) available in New Zealand: apixaban (Eliquis) or dabigatran (Pradaxa). However, since the mechanism of action is similar to rivaroxaban, a precautionary approach is recommended with these DOACs. Please review all patients with APS requiring anticoagulant therapy and consider switching those taking DOACs to other therapy, such as warfarin.

References

1. Pengo V, Denas G, Zoppellaro G, et al. 2018: Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. *Blood* 132(13): 1365–71. DOI: 10.1182/blood-2018-04-848333 (accessed 22 July 2019).

Artemisia annua and QT interval prolongation

Key Messages

- Patients taking natural health products containing *Artemisia annua* may be at risk of QT interval prolongation.
- Advise patients at risk of QT interval prolongation to carefully check the ingredients of any natural health products or dietary supplements before use.
- Patients taking QT-prolonging medicines or with other risk factors for QT interval prolongation should avoid taking products containing *Artemisia annua*.

Introduction

Artemisia annua (also known as *Qing hao*, Sweet Annie or Sweet Wormwood) dried herb or extract are constituents in several natural health products available in New Zealand.

Artemisinin is a constituent of *Artemisia annua*, and its derivatives form the basis of the artemisinin-based combination therapies (ACTs) now recommended by WHO for treating certain types of malaria[1].

QT interval prolongation is associated with ACTs[2–4]. Patients who use natural health products containing *Artemisia annua* may also be at increased risk of developing a prolonged QT interval. The risk is greater in patients taking other QT-prolonging medicines, or with other risk factors for long QT syndrome (LQTS).

Products containing *Artemisia annua* extract

Several products known to contain *Artemisia annua* extract have been prominently marketed in New Zealand. These products contain *Artemisia annua* herb or extract, either alone or in combination with other ingredients such as curcumin (turmeric)[5,6].

New Zealand does not have a register of herbal medicines or an approval system for natural health products so a complete list of products containing *Artemisia annua* dried herb or extract cannot be provided here.

Advise patients at risk of prolonged QT interval to carefully check the ingredients of any natural health product or dietary supplement before use. Patients taking QT-prolonging medicines or with other risk factors for LQTS should avoid taking products containing *Artemisia annua*.

Drug-induced QT interval prolongation

Drug-induced QT interval prolongation is discussed in a previous issue of *Prescriber Update*: **www.medsafe.govt.nz/profs/PUArticles/DrugInducedQTProlongation.htm**.

An up-to-date list of drugs that cause QT interval prolongation is available at **https://crediblemeds.org/healthcare-providers/**

New Zealand case reports

The Centre for Adverse Reactions Monitoring (CARM) has received two reports of QT interval prolongation in individuals who were taking Arthrem (*Artemisia annua* extract in grapeseed oil): CARM ID numbers 122230 and 133141.

References

1. World Health Organization. 2015. *Guidelines for the Treatment of Malaria* (3rd edition). World Health Organization: Geneva. URL: www.who.int/malaria/publications/atoz/9789241549127/en/ (accessed 23 July 2019).
2. CredibleMeds. 2019. *Combined list of drugs that prolong QT and/or cause torsades de pointes (TDP).* URL: https://crediblemeds.org/index.php/new-drug-list (accessed 23 July 2019).
3. Funck-Brentano C, Ouologuem N, Duparc S, et al. 2019. Evaluation of the effects on the QT-interval of 4 artemisinin-based combination therapies with a correction-free and heart rate-free method. *Scientific Reports* 9(1): 883. DOI: 10.1038/s41598-018-37113-5 (accessed 23 July 2019).
4. World Health Organization. 2017. *The cardiotoxicity of antimalarials*. WHO Evidence Review Group Meeting, 13–14 October 2016, Varembe Conference Centre, Geneva, Switzerland. URL: www.who.int/malaria/mpac/mpac-mar2017-erg-cardiotoxicity-report-session2.pdf (accessed 23 July 2019).
5. Promisia. 2019. *Arthrem*. URL: http://arthrem.co.nz/Arthrem/Product (accessed 24 July 2019).
6. Good Health. 2019. *Turmeric Extra Strength*. URL: www.goodhealth.co.nz/products/detail/turmeric-extra-strength (accessed 24 July 2019).

MARC's remarks: June 2019 Meeting

The Medicines Adverse Reactions Committee (MARC) met on 13 June 2019 to discuss a number of medicine-related safety issues.

Based on their review of cases reported to the Centre for Adverse Reactions Monitoring (CARM), the MARC recommended that:

- Medsafe communicates with the coroner to request an update on CARM case 132344, where a patient was inadvertently administered Botox instead of Dysport (see page 48 for an article describing the differences between the **botulinum toxin type A** products available in New Zealand)
- the Chair of the MARC communicates with the New Zealand Formulary to request that their **Fleet enema** monograph is updated to include information about the risk of hyperphosphataemia.

The MARC discussed **trimethoprim** use in patients aged 65 years or older. The MARC recommended that Medsafe includes an article about medicines that can interfere with creatinine measurement/excretion in a future edition of *Prescriber Update*.

The MARC discussed **carbimazole** and congenital malformations. The MARC recommended that the carbimazole data sheet and consumer medicine information are strengthened with additional information regarding contraception, and the risk of congenital malformations when carbimazole is taken during pregnancy.

The MARC discussed **fluoroquinolone** use and aortic aneurysm/dissection. The MARC recommended that the fluoroquinolone data sheets are updated to include information about this risk. The MARC also recommended that Medsafe includes an article about the risk of aortic aneurysm/dissection with fluoroquinolone use in a future edition of *Prescriber Update.*

The MARC discussed a potential drug-drug interaction between **nortriptyline** and **sertraline**. The MARC recommended that the tricyclic antidepressant (TCA) and selective serotonin reuptake inhibitor (SSRI) data sheets are updated with information about the risk of serotonin syndrome when these classes of medicines are used concomitantly.

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

Biotin beware!

Key messages

- Biotin may interfere with some laboratory tests, such as hormone tests and cardiovascular diagnostic tests.
- Consult laboratory personnel when ordering laboratory tests in patients taking biotin.

Biotin may interfere with laboratory tests that are based on biotin technology, leading to either falsely decreased or falsely increased test results, depending on the assay[1,2]. Incorrect test results may lead to inappropriate patient management or misdiagnosis[2].

Many laboratory tests that use biotin technology are potentially affected, including but not limited to cardiovascular diagnostic tests and hormone tests[2]. The risk of interference is higher in children and patients with renal impairment and increases with higher doses[1].

Multivitamins, including prenatal multivitamins, biotin supplements, and dietary supplements for hair, skin, and nail growth contain biotin at levels that may interfere with laboratory tests[1,2]. Biotin may be labelled as Vitamin B7 or Vitamin H in these products.

Consult laboratory personnel when ordering laboratory tests in patients taking biotin[1].

References

1. European Medicines Agency. 2019. *PRAC recommendations on signals – Adopted at the 14–17 January 2019 PRAC meeting*. URL: ema.europa.eu/en/documents/prac-recommendation/prac-recommendations-signals-adopted-14-17-january-2019-prac-meeting_en.pdf (accessed 19 July 2019).
2. US Food and Drug Administration. 2017. *The FDA warns that biotin may interfere with lab tests: FDA Safety Communication*. URL: https://www.fda.gov/medical-devices/safety-communications/fda-warns-biotin-may-interfere-lab-tests-fda-safety-communication (accessed 22 July 2019).

Pharmacy quality audits

Key messages

- Pharmacy premises in New Zealand are audited by Medsafe to ensure pharmacy services to the public meet the required standards.
- In early 2018 Medsafe rolled out inspection audits nationwide as the next step in the implementation of the risk-based Pharmacy Quality Audit Framework.
- Medsafe was pleased by the continued trend of improvement in performance for the January to March 2019 quarter. Medsafe looks forward to seeing an increase in the rate of improvement.

The Medicines Control team within Medsafe is responsible for regulating the medicine supply chain in New Zealand. As part of this function, Medsafe audits pharmacy premises to ensure that the pharmacy services to the public meet the required standards.

This article provides a brief overview of the:

- types of Pharmacy Quality Audits
- findings from January to March 2019
- some preliminary findings from follow-up audits conducted between April and early June 2019.

Pharmacy Quality Audit Framework

The roll out of unannounced inspection audits nationwide in early 2018 marked a significant step in the move to a fully risk-based pharmacy quality audit framework. The framework now includes two main types of audit.

- Full pharmacy quality audit – an audit assessing all services provided from the premises. It may include up to 67 criteria. At least 15 working days' notice are given prior to the audit.
- Standard inspection audit – a shorter audit focussing on the 10 risk-based criteria (Table 1). These are unannounced audits.

During an audit, the Medsafe auditor assesses each criterion and assigns a rating (ranging from 'Leading Practice' through to 'Unattained Critical', this being the highest risk).

Information, including the ratings, forms part of the audit framework, and allows Medsafe to monitor pharmacy performance, and to focus resource where further action is needed.

Each quarter, Medsafe updates the pharmacy sector with an overview of current audit trends and findings. The update document is sent to all pharmacies in New Zealand and is hosted on the members' section of the Pharmaceutical Society of New Zealand's website. In addition, Medsafe established a sector response group including representatives of the District Health Boards, Pharmacy Council of New Zealand, Pharmaceutical Society of New Zealand, Pharmacy Guild, and other pharmacy sector groups, to provide a forum for discussions of trends identified, and to promote continuous quality improvement in the sector.

Table 1: Risk-based audit criteria (as at August 2019)

Criterion	Description
1.02.01	All staff are suitably qualified for the pharmacy services provided from the premises.
2.02.01	There is ready access at the premises to all the required pharmacy equipment.
3.03.02	Appropriate corrective actions are implemented, documented and reviewed contributing to continuous quality improvement.
4.01.02	Controlled drugs requiring storage in a safe, are securely held in an approved controlled drugs safe.
4.01.04	Fridge temperatures are consistently maintained between 2–8°C.
5.01.02	Prescription medicines are supplied in accordance with regulatory and professional requirements.
5.02.01	An approved form of controlled drugs register is appropriately and accurately maintained, and retained on the premises for four years.
5.05.04	Compounding records for individually compounded products are appropriately maintained and stored on the premises for at least three years.
5.07.04	Medicines requiring supply by an accredited pharmacist are recorded, sold and labelled in accordance with regulatory and professional requirements.
5.10.03	Compliance packaging is labelled sufficiently in accordance with regulatory and professional requirements.

Pharmacy quality audit updates: January to March 2019

Medsafe is pleased by the continued trend of improvement in performance in the January to March 2019 quarter. Medsafe looks forward to seeing an increase in the rate of improvement. Community pharmacies are an integral part of the health care system, and thus it is essential that pharmacy practice meets the required standards to contribute to provision of a safe service to patients.

Follow-up inspection audits

Recently Medsafe conducted follow-up inspection audits at pharmacies where high or critical risk had been identified at a previous audit. The follow-up audit only assessed compliance with these criteria. The preliminary findings demonstrated a significant improvement with around two-thirds of the audit criteria found to be fully compliant.

Medsafe acknowledges the significant effort made by many of these pharmacies to raise and sustain their performance.

Medsafe continues to work closely with DHBs, Pharmacy Council of New Zealand, Pharmaceutical Society of New Zealand, and pharmacy sector to help improve performance further.

For any queries regarding the risk-based audit framework of pharmacies, please contact Medicines Control (**medicinescontrol@health.govt.nz**).

Gathering knowledge from adverse reaction reports: September 2019

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: 131310 **Age:** 76 **Gender:** Female **Medicine(s):** Zoledronic acid **Reaction(s):** Uveitis, malaise	A 76-year-old woman developed malaise and uveitis after an infusion of zoledronic acid.
	Malaise and uveitis are listed as common and rare adverse reactions, respectively, in the Aclasta data sheet (**www.medsafe.govt.nz/profs/Datasheet/a/Aclastainf.pdf**).
CARM ID: 132223 **Age:** 79 **Gender:** Female **Medicine(s):** Pregabalin **Reaction(s):** Peripheral oedema, sleep disturbed, (withdrawal reaction)	A 79-year old patient taking pregabalin for neuropathic pain experienced gradual onset of ankle oedema. Pregabalin was discontinued over three weeks and the ankle oedema resolved within four weeks. However, the patient experienced disturbed sleep for 10 days after discontinuation.
	The Pregabalin Pfizer data sheet states that withdrawal symptoms, including insomnia, have been observed in some patients after discontinuation of short-term and long-term treatment. Peripheral oedema is listed as a common adverse effect (**www.medsafe.govt.nz/profs/Datasheet/l/Lyricacaps.pdf**).
CARM ID: 132313 **Age:** 75 **Gender:** Male **Medicine(s):** Escitalopram **Reaction(s):** Ulcerative colitis, haemorrhagic diarrhoea	A 75-year-old man with a history of ulcerative colitis experienced a flare-up of his colitis with bloody diarrhoea shortly after starting escitalopram.
	The Escitalopram Apotex data sheet lists diarrhoea as a common adverse reaction. Abnormal bleeding, predominantly of skin and mucous membranes is listed as uncommon. Escitalopram should be used with caution in patients with a history of abnormal bleeding or those with predisposing conditions (**www.medsafe.govt.nz/profs/Datasheet/e/EscitalopramApotextab.pdf**).

Case details[a]	Reaction description and data sheet information[b]
CARM ID: 132517 **Age:** 59 **Gender:** Female **Medicine(s):** Amiodarone, atorvastatin **Reaction(s):** Blood creatine kinase increased, drug interaction, muscular weakness	A 59-year-old woman on long-term atorvastatin experienced muscle weakness and increased blood creatine phosphokinase (CPK) levels after commencing amiodarone. An amiodarone-atorvastatin drug interaction was suspected. Her symptoms improved upon discontinuation of atorvastatin.
	Atorvastatin is metabolised by cytochrome P450 3A4 (CYP3A4), and amiodarone is a CYP3A4 inhibitor. The Aratac data sheet states that the risk of muscular toxicity is increased by concomitant administration of amiodarone with statins metabolised by CYP 3A4, including atorvastatin (**www.medsafe.govt.nz/profs/Datasheet/a/aratactab.pdf**). The Lorstat data sheet states that concomitant use of CYP3A4 inhibitors can lead to increased atorvastatin plasma concentrations. Myopathy is listed as a rare adverse event in the Lorstat data sheet and should be considered in any patient with diffuse myalgias, muscle tenderness or weakness and/or marked elevation of creatine kinase (CK). Discontinue atorvastatin if markedly elevated CPK levels occur or myopathy is diagnosed or suspected (**www.medsafe.govt.nz/profs/Datasheet/l/lorstattab.pdf**).
CARM ID: 132541 **Age:** 21 **Gender:** Female **Medicine(s):** Ethinylestradiol + norethisterone **Reaction(s):** Hepatic enzymes increased, jaundice, lethargy, nausea, pruritus	A 21-year-old female taking long-term ethinylestradiol + norethisterone experienced nausea, lethargy, jaundice, itch and deranged liver function tests. Abdominal ultrasound and infection screen were normal.
	The Norimin data sheet states that certain endocrine and liver function tests and certain blood components may be affected by hormonal contraceptives, but abnormal liver function tests may indicate organ damage. Nausea (common) pruritus (frequency not known), cholestatic jaundice (rare), hepatocellular injury (eg, hepatitis, hepatic function abnormal; frequency not known) are listed as undesirable effects. Early identification can decrease the severity of hepatotoxicity when the medicine is discontinued (**www.medsafe.govt.nz/profs/Datasheet/BrevinorNorimintab.pdf**).

Notes:

a. Only the medicines suspected to have caused the reaction are listed in the table.

b. 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) (**www.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).

Quarterly summary of recent safety communications

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

Date	Communication	Topic
16 August 2019	Monitoring Communication	**Cathejell Lignocaine** 2% Gel and reports of issues when using this medicine
9 August 2019	Monitoring Communication	**Tramadol** and opioid effects in breastfeeding babies – monitoring extended to 30 November 2019
9 August 2019	Dear Healthcare Professional Letter	**Femme-Tab** (PDF 174 KB, 1 page) – brought in to cover stock shortage of combined oral contraceptive products (**Microgynon, Levlen**); information about blister pack differences
1 August 2019	Alert Communication	Medsafe is issuing a warning to consumers to stop taking **Go lean Detox** and Go Detox – statement under section 98 of the Medicines Act 1981
31 July 2019	Monitoring Communication	Update – **Breast implants** and anaplastic large cell lymphoma
17 July 2019	Dear Healthcare Professional Letter	**Ranbaxy-Cefaclor** (PDF 222KB , 1 page) – Supply disruption for **Cefaclor** oral suspension and **Acarbose** tablets: difference in reconstitution volume for **Keflor** granules
3 July 2019	Dear Healthcare Professional Letter	**FluQuadri** (PDF 109 KB, 2 pages) – Additional supply of FluQuadri influenza vaccine: differences in labelling and package inserts
28 June 2019	Publications	Consumer Information Leaflet – Taking **Lithium** during pregnancy (PDF 319 KB, 2 pages)
11 June 2019	Dear Healthcare Professional Letter	**Xiaflex®** (collagenase clostridium histolyticum) product discontinuation from 28 June 2019 (PDF 231 KB, 2 pages)

Lamotrigine and a rare immune system reaction: Haemophagocytic lymphohistiocytosis (HLH)

Key messages

- Haemophagocytic lymphohistiocytosis (HLH) has been reported in patients taking lamotrigine.
- HLH is a very serious, possibly life-threatening, reaction arising from excessive activation of the body's immune system.

What is haemophagocytic lymphohistiocytosis (HLH)?

HLH is a rare but life-threatening syndrome caused by excessive immune system activation[1,2]. Persistent fever is usually present, and several organs can be affected[2].

HLH is more common in young children aged under 18 months, but also occurs in older children and adults[3]. Patients with HLH may have a predisposing genetic defect, and/or an immunologic trigger such as infection[3].

Typical clinical features include fever, hepatosplenomegaly, rash, lymphadenopathy, neurologic symptoms, cytopenias, high serum ferritin, and liver function abnormalities[3]. Early diagnosis and prompt treatment are essential to improve patient outcomes and reduce mortality[2,3].

HLH and lamotrigine

Internationally, HLH has been reported in patients taking lamotrigine[2].

In New Zealand, lamotrigine is indicated for the treatment of epilepsy in children (from age 2 years) and adults, and bipolar disorder in adults[1]. HLH is included in the warnings and precautions section of the Logem data sheet[1]. Symptoms usually occur within four weeks of starting treatment[1]. Lamotrigine should be discontinued promptly if HLH is suspected.

Up to June 2019, the Centre for Adverse Reactions Monitoring (CARM) had not received any reports of HLH associated with lamotrigine.

References

1. Mylan New Zealand Ltd. 2018. *Logem New Zealand Data Sheet* October 2018. URL: www.medsafe.govt.nz/profs/Datasheet/l/logemtab.pdf (accessed 24 June 2019).
2. US Food and Drug Administration. 2018. *FDA Drug Safety Communication: FDA warns of serious immune system reaction with seizure and mental health medicine lamotrigine (Lamictal).* URL: www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-serious-immune-system-reaction-seizure-and-mental-health (accessed 24 June 2019).
3. McClain KL, Eckstein O. 2019. Clinical features and diagnosis of hemophagcytic lymphohistiocytosis. In: *UpToDate*. 11 July 2019. URL: www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis (accessed 23 July 2019).

Medicines classification update

Melatonin

At the 61st meeting of the Medicines Classification Committee (MCC) in November 2018, the MCC recommended that melatonin should be reclassified to 'prescription except when'.

The new classification for melatonin was implemented on 24 June 2019[1].

Melatonin is now classified as:

> Prescription except when supplied in medicines for oral use containing 3 mg or less per immediate release dose unit, or 2 mg or less per modified release dose unit, when sold in the manufacturers original pack that has received consent from the Minister of Health or the Director General for the treatment of primary insomnia for adults aged 55 years or older for up to 13 weeks by a registered pharmacist.

This new classification means that melatonin is a prescription medicine except when supplied under the conditions described in the classification statement. Pharmacists may only supply melatonin if they meet the competency requirements set by the Pharmacy Council.

Updates following the 62nd meeting of the Medicines Classification Committee

At the 62nd meeting held on 11 April 2019, the MCC recommended several changes to the classification of medicines. These included:

- the classification of **budesonide** and **fluticasone** should harmonise with Australian requirements. The limit on the primary pack size for both these substances and the limit on the dose per actuation for budesonide should be removed from the pharmacy-only classification statement
- the following new chemical entities should be classified as prescription medicines: brigatinib, crisaborole, lanadelumab, romosozumab, safinamide, tilmanocept, tivozanib.

These classifications were implemented on 12 July 2019[2].

The MCC considered applications to reclassify ropivacaine and bupivacaine. The MCC requested further information from the applicant.

More information

The Medsafe website has information on the classification process and minutes of the MCC meetings (**www.medsafe.govt.nz/committees/mcc.asp**). You can search the classification database to check the classification of an active ingredient (**www.medsafe.govt.nz/profs/class/classintro.asp**).

References

1. New Zealand Gazette. *Classification of Medicines* 24 June 2019. Notice Number: 2019-go2911. URL: https://gazette.govt.nz/notice/id/2019-go2911 (accessed 15 July 2019).
2. New Zealand Gazette. *Classification of Medicines* 12 July 2019. Notice Number: 2019-go3281. URL: https://gazette.govt.nz/notice/id/2019-go3281 (accessed 15 July 2019).

We need your help!

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

Medicine	Potential safety issue	Active monitoring ends
Denosumab	Risk of infections	30 November 2019
Tramadol	Opioid effects in breastfeeding babies	Extended to 30 November 2019

- 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 (**www.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.

Recent approvals of medicines containing a new active ingredient

For the period 16 April 2019 to 15 July 2019.

Trade name (Active ingredient)	Dose form and strength(s)	Therapeutic area
Jinarc (tolvaptan)	Tablet combination[a] 45 mg + 15 mg 60 mg + 30 mg 90 mg + 30 mg Tablet 15 mg 30 mg	Autosomal dominant polycystic kidney disease (ADPKD)
Kisqali (ribociclib)	Film coated tablet 200 mg	Breast cancer
Repatha (evolocumab)	Solution for injection 140 mg pre-filled syringe 140 mg pre-filled pen	Hypercholesterolaemia
Viberzi (eluxadoline)	Film coated tablet 100 mg	Irritable bowel syndrome with diarrhoea (IBS-D)

a. This product comes in fixed-dose combinations to facilitate the split-dose regimen.

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

Summary of spontaneous reports for meningococcal vaccines

Introduction

The Northland Meningococcal W vaccination programme started in December 2018 and ended in April 2019. This was a targeted programme, using meningococcal ACYW vaccines, to combat a community outbreak of meningococcal W disease in Northland. In addition, Bexsero (meningococcal B vaccine) was approved for use in New Zealand in July 2018.

Here we provide an overview of adverse reactions reported for these meningococcal vaccines between July 2018 and April 2019.

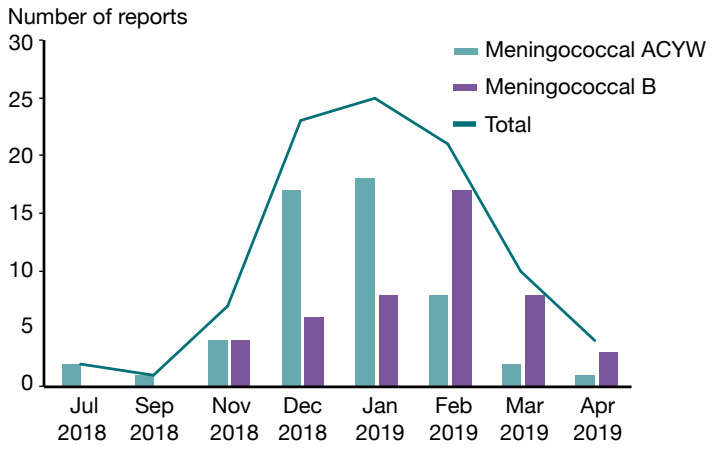
Spontaneous reports received between July 2018 and April 2019

The Centre for Adverse Reactions Monitoring (CARM) received 93 case reports of adverse events following immunisation (AEFI) for meningococcal vaccines between July 2018 and April 2019. There were 53 reports for meningococcal ACYW vaccines (Menactra and Nimenrix) and 46 reports for meningococcal B vaccine (Bexsero) during this time period. (Note some patients received more than one meningococcal vaccine so the number of case reports does not equal the sum of the vaccine reports.) Figure 1 shows the distribution of these reports over the time period.

Of the 93 reports, 92 were not serious and 1 was reported as life-threatening in a patient who had received Menactra (CARM ID 131300). The patient started to experience anaphylactic symptoms during the post-vaccination observation period, which the nurse promptly dealt with.

The most commonly reported reactions were injection site inflammation, arm pain and fever (Figure 2); these reactions are listed in the vaccine data sheets[1–3]. The largest number of reports were received for patients aged 17 years and younger (Figure 3) and from Northland (Figure 4). Reporting may have been higher in Northland due to the Meningococcal W outbreak vaccination programme. The Northland vaccination campaign was run from 5 December 2018 to 16 April 2019 and offered free meningococcal ACYW vaccinations to children aged 9 months to under 5 years and those aged 14 years to 19 years. It is not uncommon to see an increase in AEFI reports during mass vaccination campaigns or when new vaccines are introduced to the national immunisation schedule.

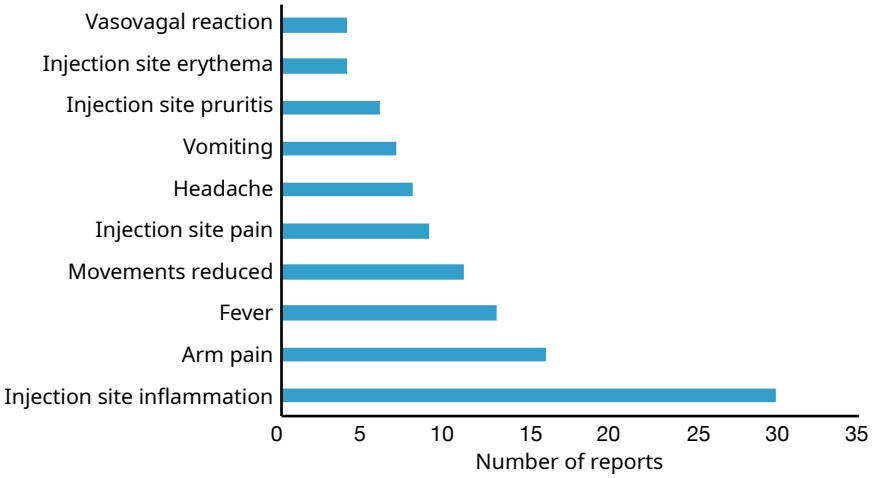
Figure 1: Number of reports* received by the Centre for Adverse Reactions Monitoring for meningococcal ACYW and B vaccines, July 2018–April 2019



* Some patients received more than one meningococcal vaccine so the total number of reports does not equal the sum of the meningococcal ACYW and B reports.

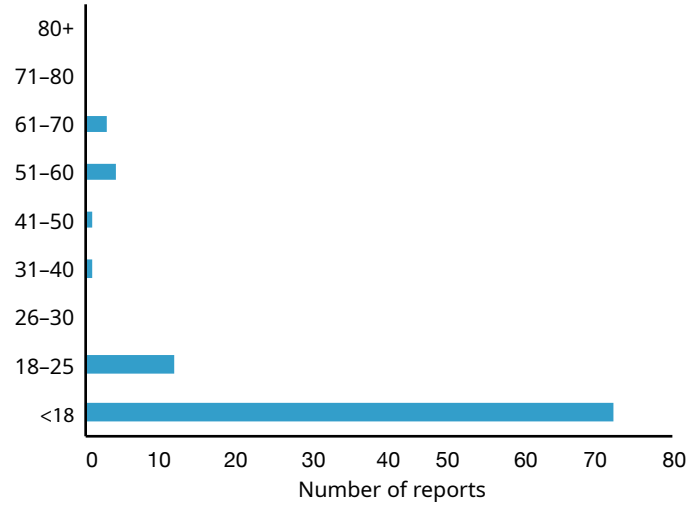
Source: Centre for Adverse Reactions Monitoring

Figure 2: Ten most frequently reported adverse reaction terms for meningococcal ACYW and B vaccines, July 2018–April 2019



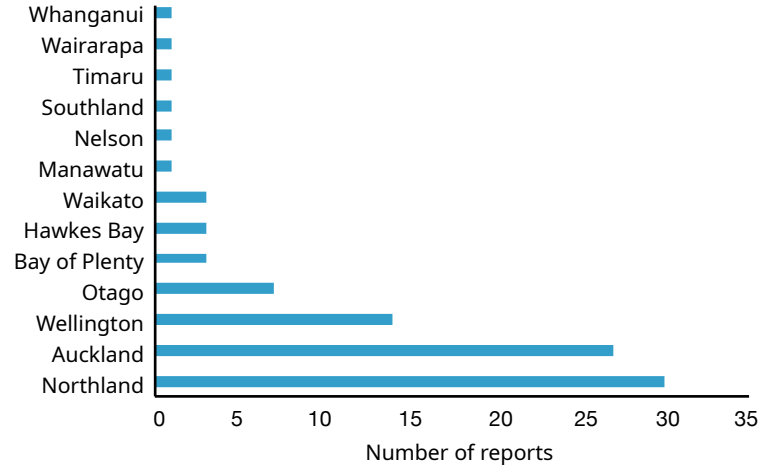
Source: Centre for Adverse Reactions Monitoring

Figure 3: Number of reports by age for adverse reactions to meningococcal ACYW and B vaccines, July 2018–April 2019



Source: Centre for Adverse Reactions Monitoring

Figure 4: Number of reports per region for adverse reactions to meningococcal ACYW and B vaccines, July 2018–April 2019



Source: Centre for Adverse Reactions Monitoring

References

1. sanofi-aventis New Zealand Pty Ltd. 2018. Menactra New Zealand Data Sheet 5 July 2018. URL: www.medsafe.govt.nz/profs/Datasheet/m/menactrainj.pdf (accessed 5 August 2019).
2. Pfizer New Zealand Limited. 2019. Nimenrix New Zealand Data Sheet 12 January 2019. URL: www.medsafe.govt.nz/profs/Datasheet/n/nimenrixinj.pdf (accessed 5 August 2019).
3. GlaxoSmithKline NZ Limited. 2018. Bexsero New Zealand Data Sheet 12 October 2018. URL: www.medsafe.govt.nz/profs/Datasheet/b/bexseroinj.pdf (accessed 5 August 2019).

Medicinal Cannabis Scheme: An update from the Ministry of Health

Key messages

- Medicinal Cannabis regulations will be in place by 18 December 2019 and the Scheme commences in the first quarter of 2020.
- Professional organisations and specialties are encouraged to continue providing guidance to their members on medicinal cannabis.
- The Ministry of Health will make available to medical practitioners (doctors) a list of unapproved medicinal cannabis products that meet minimum quality standards.
- Manufacturers will be encouraged to provide product information with their medicinal cannabis products.
- Once the regulations have been passed, the Ministry will look at the provision of other guidance material to healthcare professionals.

The Medicinal Cannabis Scheme

The Government has committed to establishing a Medicinal Cannabis Scheme (the Scheme) to improve access to quality medicinal cannabis products. The Scheme will do this through:

- enabling the commercial cultivation of medicinal cannabis and the manufacture of medicinal cannabis products in New Zealand
- setting quality standards for medicinal cannabis products so that medical practitioners can prescribe them with more confidence.

A regulatory system, with controls on the cultivation of cannabis and the manufacture and supply of medicinal cannabis products, is needed to support the Scheme. The regulations are being developed to establish the regulatory system.

Consultation and next steps

Interest in the proposed Medicinal Cannabis Scheme was heightened with publication of the consultation document in July. Submissions closed on 7 August and, since that time, the Ministry of Health has been analysing the responses as part of the process of developing final proposals for Government consideration. The proposals will go to the Medicinal Cannabis Advisory Group before being presented to the Government. The Medicinal Cannabis regulations will be in place by 18 December 2019, and the Scheme will start in the first quarter of 2020.

Industry, patients and prescribers all need to be confident about medicinal cannabis products. All medicinal cannabis products under the Scheme will need to meet minimum standards of quality.

The Ministry of Health recognises that in the early stages of the Scheme, most medicinal cannabis products are likely to be 'unapproved' and will be unable to be advertised. The Ministry will, therefore, make available to doctors a list of unapproved medicinal cannabis products that meet quality standards. Prescribers are reminded that they are responsible for the quality safety and efficacy of unapproved medicines used in their patients.

Clinical data on the use of medicinal cannabis for certain conditions is incomplete but developing.

To assist medical practitioners in their decision to prescribe, the Ministry has suggested manufacturers may wish to provide product information sheets with their products, setting out what is known about them. The Ministry of Health will also provide information to healthcare professionals to assist education and training.

More information

For more information about the Medicinal Cannabis Scheme, see the Ministry of Health website (**www.health.govt.nz/our-work/regulation-health-and-disability-system/medicines-control/medicinal-cannabis/medicinal-cannabis-scheme**).

Report Adverse Drug Reactions

Reporting adverse reactions contributes to the safety of medicines in New Zealand.

If you think your patient has had an adverse reaction to a medicine, report it to CARM.

Online reporting is easiest (**https://nzphvc.otago.ac.nz/reporting/**).

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

Acknowledgement
Andi Shirtcliffe, Ministry of Health
Chris Millar, Ministry of Health
Associate Professor David Reith, University of Otago
Janet Mackay, PHARMAC
Dr Michael Tatley, Centre for Adverse Reactions Monitoring
Dr Ruth Savage, Centre for Adverse Reactions Monitoring

Clinical Advisor Dr Geraldine Hill

Group Manager Chris James

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

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

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