Prescriber Update

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Contents

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Spotlight on dulaglutide

Key messages

- Dulaglutide is a glucagon-like peptide 1 (GLP-1) receptor agonist indicated for glycaemic control and risk reduction of major cardiovascular events in adults with type 2 diabetes.
- Gastrointestinal side effects (such as nausea, diarrhoea and vomiting) are common.
- Serious side effects can occur, such as acute pancreatitis, cholecystitis, hypoglycaemia and acute kidney injury secondary to dehydration.
- The risk of hypoglycaemia is increased when dulaglutide is used with insulin or sulfonylureas. Consider lowering the dose of these medicines when co-prescribing with dulaglutide.

This article gives an overview of dulaglutide – how it works, how it is used and its adverse reactions.

Indications and mechanism of action[1,2]

Dulaglutide is a long-acting glucagon-like peptide 1 (GLP-1) receptor agonist. It is indicated for improvement of glycaemic control and reduction in the risk of cardiovascular events in adults with type 2 diabetes.

GLP-1 receptor agonists improve glycaemic control through:

- increasing the amount of insulin released by the pancreas – this helps the body to use and store glucose
- reducing the amount of glucagon released by the pancreas – this reduces the amount of glucose produced by the liver
- slowing gastric emptying – food is absorbed from the stomach more slowly, reducing appetite and lowering blood glucose after a meal.

Products in New Zealand

One dulaglutide product (Trulicity) is currently approved and available in New Zealand. It is given once a week as a subcutaneous injection.[1]

Trulicity can be used as a monotherapy or in combination with other glucose-lowering medicines, such as metformin, insulin and sulfonylureas.[1]

Other considerations for use

Dipeptidyl peptidase 4 (DPP-4) inhibitors (eg, vildagliptin) are another class of medicines used to treat type 2 diabetes. DPP-4 inhibitors have a similar mechanism of action to dulaglutide. Clinical guidelines state that dulaglutide and DPP-4 inhibitors should not be given together due to the potential for adverse effects without any additional benefit for diabetes control.[3,4]

Adverse drug reactions[1]

The most frequently reported adverse reactions with dulaglutide are gastrointestinal events (nausea, vomiting, diarrhoea, stomach pain, decreased appetite and dyspepsia).

Some of the more serious adverse effects described in the dulaglutide data sheet are discussed below. Remind patients to seek medical attention if they experience any symptoms of concern.

Gastrointestinal adverse reactions

Gastrointestinal adverse reactions are common in people taking dulaglutide and peak in the first few weeks of treatment. While these reactions are typically mild to moderate in severity, there have been reports of these reactions leading to dehydration and acute kidney injury.

Dulaglutide is not recommended in patients with severe pre-existing gastrointestinal disease, including severe gastroparesis.

Elevated pancreatic enzymes and pancreatitis

Elevated pancreatic enzymes can occur in people taking dulaglutide. While this alone does not always indicate pancreatitis, cases of acute pancreatitis have been reported. If pancreatitis is confirmed, dulaglutide should be permanently stopped.

Cholecystitis

Cholecystitis (inflammation of the gallbladder) has been reported to occur uncommonly in people taking dulaglutide.

Hypoglycaemia

Hypoglycaemia occurs more commonly when dulaglutide is used with insulin or sulfonylureas. Consider lowering the dose of insulin or sulfonylurea to reduce the risk of hypoglycaemia.

New Zealand case reports

Up to 27 October 2023, the Centre for Adverse Reactions Monitoring (CARM) had received 54 adverse reaction reports where dulaglutide was the suspect medicine, including 36 serious reports. Most of the reports relate to the gastrointestinal system. Table 1 shows the top five most frequently reported adverse reactions.

CARM has received two reports with co-administration of dulaglutide and a DPP-4 inhibitor. The reported reactions were:

- CARM ID 142859: dyspepsia and headache
- CARM ID 145391: dizziness and sinus tachycardia.

Table 1: Top five most frequently reported adverse reactions for dulaglutide received by the Centre for Adverse Reactions Monitoring, up to 27 October 2023

Adverse reaction	Number of reports[a]
Nausea	18
Vomiting	14
Diarrhoea	14
Abdominal pain[b]	13
Pancreatitis[c]	8

a. The number of reports for each reaction adds to more than the total number of reports for dulaglutide as some people reported more than one adverse reaction

b. Includes abdominal pain, abdominal discomfort, abdominal colic and abdominal cramp

c. Includes pancreatitis and necrotising pancreatitis

Source: Centre for Adverse Reactions Monitoring, data extracted 27 October 2023

More information

- For more information about dulaglutide, see the data sheet and consumer medicines information (CMI): Search for a data sheet or CMI.
- Healthify has specific information for consumers about dulaglutide, plus more general information about type 2 diabetes and medicines to treat it.

References

1. Eli Lilly and Company (NZ) Limited. 2023. *Trulicity New Zealand Data sheet* 9 June 2023. URL: medsafe.govt.nz/profs/Datasheet/t/trulicityinj.pdf (accessed 13 October 2023).
2. Dungan K and DeSantis A. 2023. Glucagon-like peptide 1-based therapies for the treatment of type 2 diabetes mellitus. In: *UpToDate* 8 September 2023. URL: uptodate.com/contents/glucagon-like-peptide-1-based-therapies-for-the-treatment-of-type-2-diabetes-mellitus (accessed 13 October 2023).
3. bpac^{NZ}. 2022. Do not prescribe vildagliptin and dulaglutide concurrently. *Best Practice Bulletin:* Issue 61. URL: bpac.org.nz/bulletin/bestpractice/sixty-one.aspx#3 (accessed 13 October 2023).
4. New Zealand Formulary (NZF). 2023. *NZF v136: Dulaglutide* 1 October 2023. URL: nzf.org.nz/nzf_71107 (accessed 13 October 2023).

Test your knowledge: the *Prescriber Update* quiz 2023

Have you been reading Prescriber Update in 2023?

Have you kept up to date with emerging safety signals?

Test your knowledge with the end-of-year *Prescriber Update* quiz.

Answers to the quiz are on page 86 and the Medsafe website.

1. Antipsychotics can inhibit the action of which neurotransmitters, resulting in prolonged gastrointestinal time and contributing to constipation?
   a. acetylcholine, dopamine or glutamate
   b. gamma-aminobutyric acid (GABA), norepinephrine or serotonin
   c. acetylcholine, histamine or serotonin
   d. glutamate, histamine or norepinephrine
2. Unless covered by an exemption or blanket approval, which classes of controlled drugs require approval from the Minister of Health to supply, prescribe and administer?
3. Metoclopramide use in children and young adults is limited to certain conditions and as second-line therapy due to the risk of what type of side effects?
4. [Name of medicine] may be fatal if ingested by pets.
5. List the four risk factors for antidepressant withdrawal symptoms.
6. Baboon syndrome is the original name for which drug-induced rash?
7. Which of the following is the most well-known *DPYD* variant associated with dihydropyrimidine dehydrogenase deficiency?
   a. DPYD*13
   b. c.2846A>T
   c. HapB3
   d. DPYD*2A
8. True or false: Patients with evidence of corneal epithelial breakdown should have their ocular NSAID dose increased.
9. To reduce the risk of _____, consider reducing the patient's insulin dose when co-prescribing it with dulaglutide.
10. If a renally-impaired patient is being treated with cefepime and develops a new onset neurological condition, what might they be experiencing?

Discuss possible effects on uterine bleeding in people taking oral anticoagulant therapy

Key messages

- Inform patients they may experience new or worsened abnormal uterine bleeding when starting and during oral anticoagulant therapy.
- Pre-menopausal patients and those with a history of abnormal uterine bleeding may be at a higher risk of abnormal uterine bleeding with oral anticoagulant use.

From August 2022 to February 2023, Medsafe issued a Monitoring Communication to gather more information about abnormal uterine bleeding with oral anticoagulants.

This article aims to increase awareness about this specific type of bleeding with oral anticoagulant use.

Oral anticoagulants

Apixaban, dabigatran, rivaroxaban and warfarin are oral anticoagulant medicines approved in New Zealand. These medicines are used in the prevention and/or treatment of blood clots.

Bleeding is a known side effect of oral anticoagulants, resulting from the action of these medicines on the coagulation cascade. Such risks are reflected in the data sheets and consumer medicine information.[1-4]

What is abnormal uterine bleeding?[5]

Abnormal uterine bleeding (AUB) is defined as a variation from the normal menstrual cycle. This may include changes in regularity, frequency, duration and volume of flow.

AUB can be caused by structural uterine pathology (such as fibroids or cancer) or nonuterine causes (such as polycystic ovary syndrome or medicines that interfere with blood clotting, such as anticoagulants).

Heavy or prolonged uterine bleeding can interfere with daily activities, and in some cases, may lead to iron deficiency with or without anaemia.

Some individuals may be at a higher risk of AUB when taking anticoagulants[6,7]

The risk of AUB occurring with oral anticoagulant use is higher in pre-menopausal individuals and individuals with a history of AUB.

Limited data from randomised clinical trials and observational studies suggests that the uterine bleeding profile may differ across oral anticoagulants.

The risk of AUB may be higher with rivaroxaban compared to apixaban and warfarin. There is limited information for dabigatran.

Evaluate for AUB during oral anticoagulant therapy[6,7]

When starting oral anticoagulant therapy, ask patients about their current and past menstrual bleeding patterns.

Inform pre-menopausal patients that they may experience new or worsened AUB and post-menopausal patients that unexpected uterine bleeding may occur with oral anticoagulant use. Remind patients to seek medical attention if they experience these symptoms.

AUB may develop at any time during therapy. Ask about changes to uterine bleeding patterns during follow-up appointments.

If AUB occurs while on anticoagulant therapy, consider possible underlying causes (such as fibroids, endometriosis or cancer).

New Zealand case reports

During the Monitoring Communication period, the Centre for Adverse Reactions Monitoring received four reports of AUB associated with rivaroxaban. No reports were received for apixaban, dabigatran or warfarin.

Table 1 outlines the number of reports of AUB with oral anticoagulants up to 27 September 2023, including those received with the Monitoring Communication.

Table 1: Number of reports of abnormal uterine bleeding, by reported term, with oral anticoagulants reported in New Zealand, up to 27 September 2023

Reported term	Oral anticoagulant			
	Apixaban	Dabigatran	Rivaroxaban	Warfarin
Intermenstrual bleeding (bleeding between periods)	0	0	0	1
Menorrhagia (heavy bleeding)	0	0	3	2
Metrorrhagia (bleeding at irregular intervals)	0	0	1	0
Vaginal haemorrhage	0	3	2	1
Uterine haemorrhage	0	0	1	0
Total	**0**	**3**	**7**	**4**

Source: Centre for Adverse Reactions Monitoring, data extracted 27 September 2023

More information

- See the medicine data sheet and consumer medicine information (CMI) for further information about oral anticoagulants. Search for a data sheet or CMI.
- Healthify also has information for consumers about anticoagulants.

References

1. Pfizer New Zealand Limited. 2019. *Eliquis New Zealand Data Sheet* 30 August 2019. URL: medsafe.govt.nz/profs/Datasheet/e/eliquistab.pdf (accessed 30 October 2023).
2. Boehringer Ingelheim (N.Z.) Limited. 2020. *Pradaxa New Zealand Data Sheet* 11 March 2020. URL: medsafe.govt.nz/profs/Datasheet/p/Pradaxacap.pdf (accessed 30 October 2023).
3. Bayer New Zealand Limited. 2023. *Xarelto New Zealand Data Sheet* 29 May 2023. URL: medsafe.govt.nz/profs/Datasheet/x/Xareltotab.pdf (accessed 30 October 2023).
4. GlaxoSmithKline NZ Limited. 2023. *Marevan New Zealand Data Sheet* 14 March 2023. URL: medsafe.govt.nz/profs/datasheet/m/Marevantab.pdf (accessed 30 October 2023).

5. Kaunitz A. 2023. Abnormal uterine bleeding in nonpregnant reproductive-age patients: Terminology, evaluation and approach to diagnosis. In: *UpToDate* 24 July 2023. URL: uptodate.com/contents/abnormal-uterine-bleeding-in-nonpregnant-reproductive-age-patients-terminology-evaluation-and-approach-to-diagnosis (accessed 19 October 2023).
6. Godin R, Marcoux V and Tagalakis V. 2017. Abnormal uterine bleeding in women receiving direct oral anticoagulants for the treatment of venous thromboembolism. *Vascular Pharmacology* 93–5: 1-5. DOI: 10.1016/j.vph.2017.05.001 (accessed 27 June 2023).
7. Samuelson Bannow B. 2020. Management of heavy menstrual bleeding on anticoagulation. *Hematology: American Society of Hematology. Education Program* 2020(1): 533-7. DOI: 10.1182/hematology.2020000138 (accessed 27 June 2023).

Quarterly summary of recent safety communications

The table below is a summary of recent safety communications for healthcare professionals and consumers. Click on a specific topic to go to the communication.

Date	Communication	Topic
20/11/2023	Monitoring	Update – Interleukin inhibitors and the possible risk of pancreatitis
26/10/2023	Committees	Reclassification of methenamine hippurate
17/10/2023	Committees	Reclassification of low-dose cannabidiol
26/9/2023	Committees	Reclassification of naproxen
26/9/2023	Committees	Reclassification of paracetamol (liquid formulations)
25/09/2023	Alert	Consent to distribute pholcodine-containing medicines will be revoked on 12 January 2024
4/09/2023	Alert	Processing of adverse reaction reports received in New Zealand (PDF, 2 pages, 189 KB)

Recent data sheet updates: important new safety information

Table 1 below provides a list of data sheets recently updated with important new safety information. Note that this is not a comprehensive list of all recently updated data sheets, nor does it describe all changes to a particular data sheet.

Table 1: Recently updated data sheets (by active ingredient): important new safety information

Click on the specific medicine to open the data sheet.

Active ingredient(s): • Medicine(s)	Data sheet updates	
	Section*	Summary of new safety information
Amoxicillin + clavulanic acid: • Augmentin	4.4	Drug-induced enterocolitis syndrome
	4.5	Interaction with methotrexate
	4.8	As per 4.4
Bupropion + naltrexone • Contrave	4.4	Severe cutaneous adverse reactions (SCARs); Brugada syndrome (due to bupropion component)
	4.8	As per 4.4
Cabergoline: • Dostinex	4.4	Hypertension, myocardial infarction, seizures, stroke or psychiatric disorders in post-partum women treated for inhibition of lactation
	4.8	As per 4.4
Ceftriaxone: • Ceftriaxone-AFT	4.2	No dose changes in mild to moderate liver impairment; maximum dose of 2g daily in severe renal impairment
	4.3	Premature neonates, full-term neonates at risk of developing bilirubin encephalopathy, and neonates who require calcium-containing IV solutions
	4.4	Hypersensitivity reactions: before treatment, check if patient has had previous severe hypersensitivity reactions to any beta-lactam antibiotics; severe cutaneous adverse reactions (SCAR) have been reported. New warnings for: renal lithiasis; risk of bilirubin encephalopathy in neonates; lidocaine; history of gastrointestinal disease; long-term treatment; antibacterial spectrum; severe renal and hepatic insufficiency
	4.5	Calcium-containing diluents; use with oral anticoagulants
Estriol: • Ovestin Vaginal Cream • Ovestin Pessary • Ovestin Tablet	4.4	Hereditary and acquired angioedema; hepatitis C
	4.5	Use caution with co-administration of hepatitis C combination regimens
	4.8	Angioedema
Fluorouracil: • Efudix cream	4.4	May be fatal if ingested by pets
Gabapentin: • Neurontin • Nupentin	4.4	Withdrawal symptoms; women of childbearing potential/contraception
	4.6	Neonatal withdrawal syndrome; results from pregnancy study
	4.8	Withdrawal symptoms
Glecaprevir + pibrentasvir: • Maviret	4.5	May be used with products containing 20µg or less of ethinylestradiol

Active ingredient(s): • Medicine(s)	Data sheet updates Section*	 Summary of new safety information
Hydroxychloroquine: • Plaquenil	4.4	Chronic cardiac toxicity: drug-induced phospholipidosis; hepatoxicity; hepatitis B reactivation; skeletal muscle myopathy or neuropathy; renal toxicity
	4.6	Congenital malformations
	4.8	Renal phospholipidosis; hepatitis B reactivation
Levonorgestrel: • Postinor-1	4.4	Pregnancy; precautions before use; precautions after use; paediatric use (not indicated for use in prepubertal children, limited data in under 16-year-olds)
Methadone: • Methadone BNM	4.2	Treatment goals and discontinuation
	4.4	Opioid use disorder and withdrawal
	4.5	Gabapentinoids; cannabidiol
	4.8	Central sleep apnoea syndrome
	4.9	Hypoglycaemia
Methotrexate: • Methoblastin • DBL Methotrexate	4.6	Men should use contraception and/or not donate semen during treatment and for 3 months after cessation of treatment
	4.8	Brain oedema; pulmonary oedema
Ticagrelor: • Brilinta	4.2	Consider discontinuation of acetylsalicylic acid (ASA; aspirin) after 3 months in patients with acute coronary syndrome who have undergone a percutaneous coronary intervention procedure and have an increased risk of bleeding
	4.4	As per 4.2
Tobramycin • Tobra-Day	4.4	Ototoxicity in patients with mitochondrial DNA mutations
Tramadol: • Tramal	4.8	Hypoglycaemia
Vedolizumab: • Entyvio	4.6	Concentration of vedolizumab in breast milk; estimated average daily dose ingested by the infant
	4.8	Rate of infections in patients with BMI ≥30 kg/m^2 was higher than those with BMI <30 kg/m^2; updated immunogenicity data

* Data sheet sections listed in the table are: 4.2: Dose and method of administration; 4.3: Contraindications; 4.4: Special warnings and precautions for use; 4.5: Interaction with other medicines and other forms of interaction; 4.6: Fertility, pregnancy and lactation; 4.8: Undesirable effects; 4.9: Overdose

More information

To find out if sponsors have made any changes to their data sheets, see Section 10 'Date of revision of the text' (at the end of each data sheet).

- Search for a data sheet

MARC's remarks: September 2023 meeting

The Medicines Adverse Reactions Committee (MARC) convened on 14 September 2023.

The risk of toxicity in younger children and infants with **oromucosal lidocaine** containing products was reviewed. The Committee agreed that the risk of toxicity in this age group was dose related and that the greatest risk was from accidental overdose or when the package label instructions were not followed correctly. The Committee also questioned whether the current classification of these products was appropriate. The Committee recommended referral of oromucosal lidocaine products to the Medicines Classification Committee for review of the classification and whether mandatory label statements are needed.

The Committee reviewed whether there was a class association between **glucagon-like peptide-1 receptor agonists (GLP-1 RAs)** or **dipeptidyl peptidase-4 (DPP-4) inhibitors** and intestinal obstruction (including ileus). Given the known effect on gastrointestinal motility with GLP-1 RAs, the Committee recommended data sheet updates to include the risk of intestinal obstruction (including ileus) for this class of medicines. The Committee considered that more data is needed for DPP-4 inhibitors, and recommended that Medsafe publish a monitoring communication to collect more information.

The risk of QT prolongation and torsade de pointes with **acetylcholinesterase inhibitors (donepezil, rivastigmine and galantamine)** was discussed. The Committee agreed that the available evidence supports a relationship between acetylcholinesterase inhibitors and QT prolongation and torsade de pointes, and recommended data sheet updates to describe this risk.

Following new safety measures announced in the United Kingdom,[1] the Committee reviewed the available information on oral **isotretinoin** and the risk of psychiatric disorders and sexual dysfunction. The Committee noted the risk of psychiatric disorders with isotretinoin has been well-studied and a clear attributable effect has not been established. The Committee considered that the evidence supporting the risk of sexual dysfunction with isotretinoin was not strong. However, data sheet updates were recommended to include vulvovaginal dryness as an adverse reaction and modification of certain psychiatric terms. The Committee also recommended that Medsafe contact the sponsor to review the data sheet dosing information as it differs from local clinical guidelines.

See the Medsafe website for the MARC meeting minutes and the reports presented to the MARC.

Reference

1. Medicines and Healthcare products Regulatory Agency (MHRA). 2023. *Isotretinoin (Roaccutane): new safety measures to be introduced in the coming months, including additional oversight on initiation of treatment for patients under 18 years* 26 April 2023. URL: gov.uk/drug-safety-update/isotretinoin-roaccutanev-new-safety-measures-to-be-introduced-in-the-coming-months-including-additional-oversight-on-initiation-of-treatment-for-patients-under-18-years (accessed 20 October 2023).

May the fours of adverse drug reaction reporting be with you

Key messages

- There are only four requirements for a valid adverse drug reaction report: a patient identifier, medicine, reaction, reporter details.
- You don't need to be certain to report – just suspicious!
- Reporting is easiest online.

This article is a reminder about the requirements for reporting an adverse drug reaction (ADR), and how to report.

Anyone can report an ADR, including all healthcare professionals and patients/consumers.

Reporting requirements

There are only four requirements for a valid adverse drug reaction report:

1. one patient identifier (such as the patient's name, initials, date of birth, NHI number, or your own patient identifier)
2. suspect medicine(s)
3. suspected reaction(s)
4. reporter details (your name and contact details).

These are the minimum requirements for a valid report. However, including more information in your report will assist the Medical Assessors at the Centre for Adverse Reactions Monitoring (CARM) with their causality assessment.

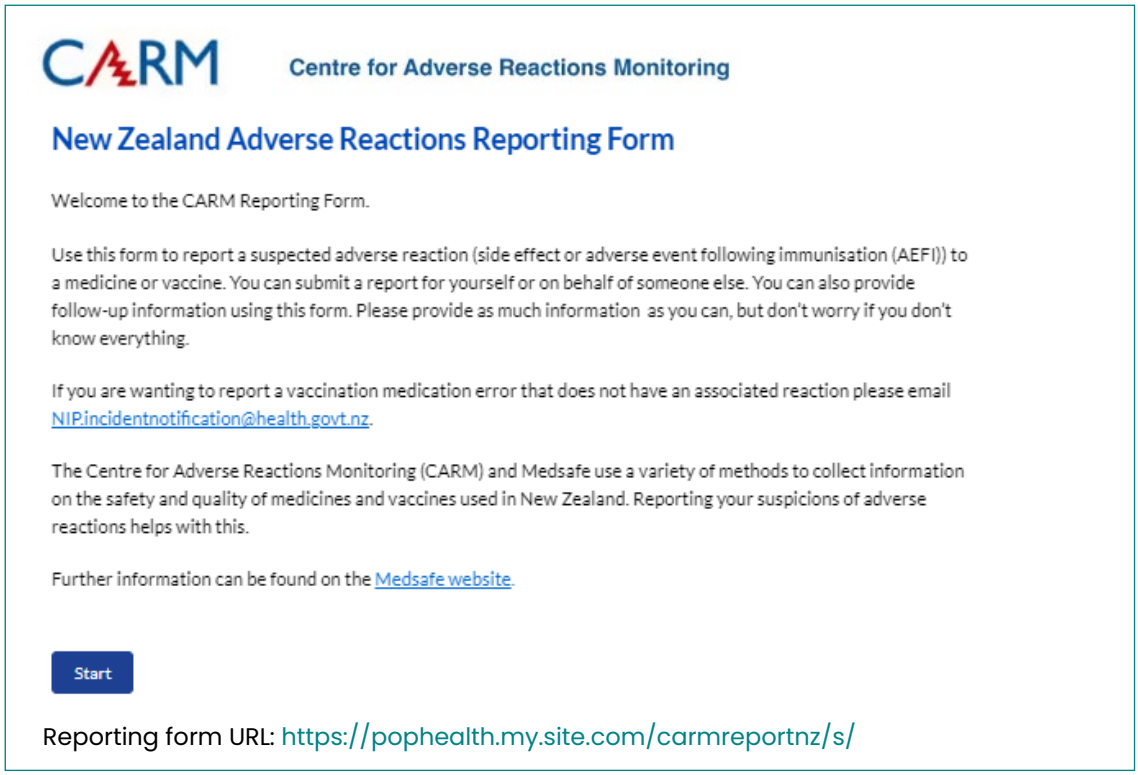
You can attach relevant clinical documents such as hospital discharge summary, specialist clinic letter or general practitioner/healthcare practitioner medical records to the report.

How to report

Reporting an ADR is easiest online. Figure 1 shows the first page of the adverse reactions reporting form.

You do not have to be certain that a medicine caused a reaction. A *suspicion* of an adverse drug reaction is all that is required to prompt a report. It is good practice to let your patient know that you will be making a report.

Figure 1: The adverse reactions reporting form



CARM Centre for Adverse Reactions Monitoring

New Zealand Adverse Reactions Reporting Form

Welcome to the CARM Reporting Form.

Use this form to report a suspected adverse reaction (side effect or adverse event following immunisation (AEFI)) to a medicine or vaccine. You can submit a report for yourself or on behalf of someone else. You can also provide follow-up information using this form. Please provide as much information as you can, but don't worry if you don't know everything.

If you are wanting to report a vaccination medication error that does not have an associated reaction please email NIP.incidentnotification@health.govt.nz.

The Centre for Adverse Reactions Monitoring (CARM) and Medsafe use a variety of methods to collect information on the safety and quality of medicines and vaccines used in New Zealand. Reporting your suspicions of adverse reactions helps with this.

Further information can be found on the Medsafe website.

Start

Reporting form URL: https://pophealth.my.site.com/carmreportnz/s/

Reporting follow-up information

If you have previously submitted an adverse drug reaction report, you can submit follow-up information as it becomes available using the same online reporting form. Please select the 'follow-up' option and include the adverse report reference number if you have it.

Want to know more?

- Each year, Medsafe publishes adverse drug reaction reporting statistics. You can find out about the ADRs reported each year in New Zealand, including what is being reported and by whom.
- Search for adverse drug reactions reported in New Zealand using the Suspected Medicine Adverse Reaction Search (SMARS).

Recent approvals: new active ingredients or new indications

New active ingredients

Table 1 shows recent approval of medicines with new active ingredients gazetted during the period 14 July 2023 to 12 October 23.

Table 1: Recent approvals of medicines with new active ingredients

Medicine	New active ingredient	Dose form: strength(s)	Therapeutic area
Galafold	Migalastat	Capsule, 123mg	Fabry disease (alpha-galactosidase A deficiency) for patients aged 16 years and older
Vabysmo	Faricimab	Solution for injection, 120mg/mL	Neovascular (wet) age-related macular degeneration (nAMD), Diabetic macular oedema (DMO)
Zonisamide Te Arai	Zonisamide	Capsule: 25mg, 50mg, 100mg	Epilepsy

New indications

Table 2 shows approved medicines with new indications for additional therapeutic areas gazetted during the period 14 July 2023 to 12 October 2023.

Table 2: Approved medicines with new indications for additional therapeutic areas

Medicine (active ingredient)	Dose form: strength(s)	New therapeutic area
Keytruda (pembrolizumab)	Concentrate for infusion: 25mg/mL (100mg/4mL)	Cutaneous squamous cell carcinoma

More information

See the Medsafe website for:

- more information about these medicines
- data sheets of currently marketed medicines
- Gazette notices for approved medicine applications.

Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE)

Key messages

- Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) is a drug-induced erythematous (red) rash involving the skin folds.
- Many medicines may cause SDRIFE, with beta-lactam antibiotics being the most commonly reported.
- SDRIFE is self-limiting and should resolve when the suspect medicine is withdrawn.

What is SDRIFE?

Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) is a drug-induced rash involving the skin folds.[1,2]

SDRIFE presents as a well-defined symmetrical V-shaped erythematous (red) rash of the gluteal region or groin, hence its original name of 'baboon syndrome'. There is often involvement of at least one other skin fold or flexural area, such as the armpit and behind the knees.[1,2]

The lack of systemic symptoms is a key characteristic of SDRIFE. Aside from the rash, the person is generally well with no other symptoms.[1]

Which medicines are associated with SDRIFE?

SDRIFE is a type IV delayed hypersensitivity reaction to a systemic medicine, appearing a few hours to a few days after medicine exposure.[1,2]

The most common medicines associated with SDRIFE are beta-lactam antibiotics (eg, penicillins, cephalosporins), which are implicated in about 50 percent of SDRIFE cases.[1]

There are many other medicines associated with SDRIFE, including non-beta-lactam antibiotics, analgesics, antifungals and iodine-containing contrast agents.[1,2]

How is SDRIFE treated?

SDRIFE is self-limiting and should resolve when the suspect medicine is withdrawn. Re-exposure to the suspect medicine usually causes SDRIFE to recur. Topical steroids may help to resolve the rash more quickly.[1]

New Zealand case reports

We are aware of three recent cases of SDRIFE reported in New Zealand (report IDs: 146385, 147293, 147315). The suspect medicines in these cases were metoprolol, cetuximab, doxycycline and ceftriaxone.

More information

For more information about SDRIFE, including images, see the DermNet website.

References

1. Dufill M. 2008. Symmetrical drug-related intertriginous and flexural exanthema. In: *DermNet* updated January 2021. URL: dermnetnz.org/topics/symmetrical-drug-related-intertriginous-and-flexural-exanthema (accessed 10 October 2023).
2. Samel A and Chu C-Y. 2023. Drug eruptions. In: *UpToDate* updated 22 February 2023. URL: uptodate.com/contents/drug-eruptions (accessed 10 October 2023).

Gathering knowledge from adverse reaction reports: December 2023

Adverse reaction reporting is an important part of medicine safety monitoring. Case reports can highlight significant safety issues with medicines and how they are used.

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: 143266 **Age:** 8 years **Gender:** Female **Medicine(s):** Dexamfetamine, atomoxetine **Reaction(s):** Drug interaction, dystonia	A child on long-term treatment with dexamfetamine was started on atomoxetine. Three months later she experienced dystonia of the jaw, which stopped following discontinuation of atomoxetine.
	Atomoxetine and dexamfetamine affect noradrenaline. The Aspen Dexamfetamine, Dexamfetamine (Noumed), Strattera and Apo-Atomoxetine data sheets describe the potential for additive or synergistic pharmacological effects with concomitant use of medicines that affect noradrenaline. The Aspen Dexamfetamine and Dexamfetamine (Noumed) data sheets also describe an interaction with atomoxetine. Concomitant use may lead to additive adverse effects, such as psychosis and movement disorders. The effects of amfetamines on mood and blood pressure may be reduced.
CARM ID: 147932 **Age**: 18 years **Gender**: Male **Medicine(s)**: Orphenadrine **Reaction(s)**: Visual hallucination, auditory hallucination	Five days after starting orphenadrine, the patient developed visual and auditory hallucinations.
	Hallucinations (frequency unknown) are listed in the Norflex data sheet.
CARM ID: 148121 **Age**: 62 years **Gender**: Female **Medicine(s)**: Sulfamethoxazole + trimethoprim **Reaction(s)**: Aseptic meningitis	Two days after starting oral sulfamethoxazole + trimethoprim (co-trimoxazole), the patient experienced nausea and vomiting. She subsequently developed a frontal headache, neck pain, photophobia and fever. She was diagnosed with aseptic meningitis. The patient had also experienced these symptoms following previous administration of co-trimoxazole.
	Aseptic meningitis is listed as a very rare adverse reaction in the Trisul data sheet.

Case details[a,b]	Reaction description and data sheet information[b,c]
CARM ID: 148278 **Age**: 3 years **Gender**: Female **Medicine(s)**: Tocilizumab **Reaction(s)**: Hepatitis	The child developed significant liver dysfunction one year after starting tocilizumab. The symptoms improved following discontinuation of tocilizumab and initiation of prednisone.
	The Actemra data sheet includes a hepatotoxicity warning in section 4.4. Serious hepatic injury, including acute liver failure, hepatitis and jaundice, has been reported between 2 weeks to more than 5 years after starting treatment.
CARM ID: 148394 **Age:** 69 years **Gender:** Male **Medicine(s):** Lisinopril, vildagliptin **Reaction(s):** Swollen tongue	The patient commenced concomitant treatment with vildagliptin and lisinopril. One month later they developed swelling of the tongue, without rash. Treatment involved steroids, antihistamines and adrenaline, plus hospital admission. Lisinopril was discontinued.
	The Lisinopril (Teva) data sheet warns that angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors (ACE-inhibitors). Patients who only experience tongue swelling may require prolonged observation as treatment with antihistamines and corticoid steroids is not always sufficient. Advise patients to immediately report any signs or symptoms suggesting angioedema and to stop taking the medicine until they have consulted with their doctor. The Galvus data sheet states that angioedema has been reported with vildagliptin, and a greater proportion of these cases were reported when vildagliptin was administered in combination with an ACE-inhibitor. See also the March 2021 *Prescriber Update* article, Vildagliptin and ACE inhibitors – increased risk of angioedema.

Notes:

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

b. 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 exactly.

c. 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).

Quiz answers

1. **c**. Antipsychotics can inhibit the action of acetylcholine, histamine or serotonin, resulting in prolonged gastrointestinal transit time, which contributes to constipation. (June 2023)
2. Unless covered by an exemption or blanket approval, individual ministerial approval is required to supply, prescribe and administer Class A, B1, B2 and C1 controlled drugs. (September 2023)
3. Due to the risk of dystonic side effects, metoclopramide use in children and young adults (aged 1 to 19 years, inclusive) is limited to certain conditions and as second-line therapy. (March 2023)
4. Efudix cream may be fatal if ingested by pets. (December 2023).
5. Antidepressant withdrawal symptoms can happen any time an antidepressant is reduced or stopped, but is more likely when:
   - antidepressants are stopped abruptly
   - antidepressants are tapered too quickly
   - someone has been taking a high dose of antidepressants
   - someone has been on antidepressants for a long time. (September 2023)
6. Baboon syndrome is the original name for symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), a drug-induced rash involving the skin folds. (December 2023)
7. **d**. DPYD*2A is the most well-known *DPYD* variant associated with DPD deficiency. Variants DPYD*13, c.2846A>T and HapB3 have also been associated with altered DPD activity. (March 2023)
8. **False**. Patients with evidence of corneal epithelial breakdown should immediately discontinue ocular NSAID treatment. (June 2023)
9. To reduce the risk of hypoglycaemia, consider reducing the patient's insulin dose when co-prescribing it with dulaglutide. (December 2023)
10. Renal impairment and a new onset neurological condition associated with cefepime may be indicative of cephalosporin-induced neurotoxicity. (March 2023)

Medsafe
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