

Prescriber Update

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In memoriam – Chip Gresham, Medicines Adverse Reactions Committee member

Dr Chip Gresham passed away unexpectedly on 12 August 2020.

Medsafe and the Medicines Adverse Reactions Committee (MARC) would like to express our shock and sadness at the passing of Dr Chip Gresham. Chip was appointed to the MARC in August 2019 for his expertise in clinical toxicology. Although Chip had only recently joined the Committee, he hit the ground running, providing helpful comments and discussions from his extensive knowledge of toxicology and health systems. Fortuitously, in his very first MARC meeting, the Committee discussed the toxicity of Bonjela, the benefits and risks of Cafergot and the risk of abuse of dextromethorphan, all issues that included a clinical toxicology component. In subsequent meetings, Chip advocated for the education of prescribers, contributed to other discussions and highlighted the importance of a CARM case, leading to its inclusion in *Prescriber Update*.

We extend our deepest sympathies to Chip's family and friends.

Kua hinga te tōtara i te wao nui a Tāne

Ka hotuhotu te manawa, ka tangi te ngākau i raro i tenei kapua pouri.

The tōtara has fallen in the great forest of Tāne

Breathe deeply and the heart cries under this dark cloud.

MARC's remarks: September 2020 meeting

The Medicines Adverse Reactions Committee (MARC) gathered through videoconference on 10 September 2020 to discuss a number of medicine-related safety issues.

The MARC discussed a very rare adverse reaction reported to the Centre for Adverse Reactions Monitoring (CARM ID: 136929), where a patient used ocular **chloramphenicol** and died months later from aplastic anaemia. The MARC recommended highlighting this case in *Prescriber Update* (see Gathering Knowledge on page 75).

The MARC discussed the potential risks of **macrolide** antibiotic use in pregnancy but considered no action was needed at this time due to limited and inconsistent evidence.

The MARC reviewed the benefits and risks of **domperidone** use in children aged under 12 years. As the evidence from the scientific literature and a post-market study showed lack of efficacy for domperidone use in this age group. The MARC recommended that the data sheet indication be revised to specify the use of domperidone in adults and children aged 12 years and older.

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

Spotlight on empagliflozin

Key messages

- Empagliflozin is indicated for the treatment of type 2 diabetes as monotherapy or in combination therapy.
- Empagliflozin prevents renal reabsorption of glucose, resulting in improved glycaemic control.
- Adequate renal function is required for empagliflozin efficacy. Assess renal function prior to initiation of empagliflozin, at least yearly during treatment, and before and after starting medicines that may reduce renal function.
- The most serious risks of harm are diabetic ketoacidosis (DKA) and necrotising fasciitis of the perineum (Fournier's gangrene). Tell patients to watch out for non-specific DKA symptoms such as nausea, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion or unusual fatigue. Fournier's gangrene symptoms include pain, redness or swelling in the genital or perineal area, fever or malaise.

The Spotlight series continues with this article on empagliflozin. PHARMAC is considering funding empagliflozin (Jardiance) and empagliflozin + metformin (Jardiamet).

Mechanism of action

Empagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor, it is indicated as a complement to diet and exercise for the improvement of glycaemic control in type 2 diabetes. SGLT2 is the main transporter that mediates reabsorption of glucose in the kidneys, from the glomerular filtrate back into the circulation. Empagliflozin improves glycaemic control by competitively inhibiting SGLT2, thereby reducing renal glucose reabsorption.¹

Empagliflozin can be used as monotherapy or in combination with other glucose lowering medicines. It is also indicated in patients with type 2 diabetes and established cardiovascular disease to reduce the risk of cardiovascular death.¹

Considerations for use

Diabetic ketoacidosis

Serious cases of diabetic ketoacidosis (DKA) have been reported in patients taking SGLT2 inhibitors, including empagliflozin.² In some of these cases, blood glucose was only slightly increased.

DKA should be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, or unusual fatigue or sleepiness, regardless of blood glucose level. Advise patients to seek immediate medical attention if they experience any of these symptoms.² If DKA is suspected, discontinue treatment with empagliflozin, evaluate the patient and initiate treatment.¹

Monitoring of ketones should be considered in situations where DKA is a risk, such as fasting prior to surgery.¹

Necrotising fasciitis of the perineum

Cases of necrotising fasciitis of the perineum (Fournier's gangrene) have been reported in patients taking SGLT2 inhibitors, including empagliflozin. This risk of this rare but life-

threatening infection should be evaluated in patients presenting with pain, redness or swelling in the genital or perineal area, fever or malaise.¹

Adequate renal function

The glucose-lowering action of empagliflozin requires adequate renal function. Renal function should be monitored prior to initiation, at least yearly during treatment, and before and after starting medicines that may reduce renal function. Empagliflozin is contraindicated in patients with severely impaired renal function (an eGFR less than 30 mL/min/1.73 m² or CrCl less than 30 mL/min).¹

Interactions

Empagliflozin may increase the diuretic effect of thiazide or loop diuretics.¹

Concomitant use with insulin or sulfonylureas may increase the risk of hypoglycaemia. A lower dose of insulin or sulfonylureas may be required.¹

Adverse drug reactions

The most commonly reported adverse reactions are hypoglycaemia (when used with insulin or a sulfonylurea), genital infections, urinary tract infection, itch, allergic skin reactions, increased urination, thirst and increased serum lipids.¹

More information

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

- [Jardiance](#)
- [Jardiamet](#)

See also '[SGLT2 Inhibitors and Diabetic Ketoacidosis](#)' in the December 2015 edition of *Prescriber Update*.

References

1. Boehringer Ingelheim (NZ) Limited. 2015. *Jardiance New Zealand Data Sheet* December 2019. URL: medsafe.govt.nz/profs/Datasheet/j/jardiancetab.pdf (accessed 22 September 2020).
2. Medsafe. 2015. SGLT2 inhibitors and diabetic ketoacidosis. *Prescriber Update* 36(4): 57–8. URL: medsafe.govt.nz/profs/PUArticles/December2015/SGLT2InhibitorsAndDiabeticKetoacidosis.htm (accessed 22 September 2020).

New COVID-19 section on the Medsafe website

We have added a new COVID-19 section to the Medsafe website, which describes our regulatory role in response to the COVID-19 pandemic. We will add more information as it becomes available.

Medsafe's COVID-19 information

Do not use oral sedating antihistamines for sedation of children

Key messages

- Oral sedating antihistamines are no longer indicated for sedation of children. This predominantly affects oral promethazine-containing medicines.
- Updated product packaging, with the changed indication of oral promethazine-containing medicines for sedation in adults only, may not appear in pharmacies for some time.
- Refer parents and caregivers looking at over-the-counter treatment options to sedate their child to a medical practitioner.

Oral sedating antihistamines are available over-the-counter and can be used for a range of conditions in both adults and children. Table 1 summarises the various uses of oral sedating antihistamines and age restrictions that apply for each use.

Importantly, oral sedating antihistamines must not be used for sedation of children due to the lack of data for this indication. Parents and caregivers looking at over-the-counter options to sedate their child must be referred to a medical practitioner.

The restriction for the use of oral sedating antihistamines for sedation to adults only is a recent change recommended by the Medicines Adverse Reactions Committee.¹ The use of oral sedating antihistamines for all other indications remains unchanged.

Oral promethazine-containing medicines are predominantly affected by this change. Data sheets and product packaging for promethazine-containing medicines are being updated so that the use for sedation is for adults only.²⁻⁴ There is likely to be a lag-time before the updated packaging appears in pharmacies.

Table 1: Uses of oral sedating antihistamines, by indication and age

Indication ^a	Age
Allergy	From 2 years of age
Nausea and vomiting (including travel sickness)	From 2 years of age
In cough and cold medicines	From 6 years of age
Insomnia	From 12 years of age
Sedation ^b	Adults only

Notes:

- Refer to the medicine data sheet or product packaging for the full wording.
- Updated product packaging for the use of promethazine-containing medicines for sedation in adults only may not appear in pharmacies for some time.

References

1. Medsafe. 2020. *Minutes of the 182nd Medicines Adverse Reactions Committee Meeting*. URL: medsafe.govt.nz/profs/adverse/Minutes182.htm (accessed 5 October 2020).
2. sanofi-aventis new zealand limited. 2019. *Phenergan New Zealand Data Sheet* February 2019. URL: medsafe.govt.nz/profs/Datasheet/p/Phenergantabelixir.pdf (accessed 5 October 2020).
3. AFT Pharmaceuticals Ltd. 2019. *Allersoothe elixir New Zealand Data Sheet* August 2019. URL: medsafe.govt.nz/profs/Datasheet/a/Allersoothetabelix.pdf (accessed 5 October 2020).
4. AFT Pharmaceuticals Ltd. 2019. *Allersoothe tablets New Zealand Data Sheet* February 2019. URL: medsafe.govt.nz/profs/Datasheet/a/Allersoothetab.pdf (accessed 5 October 2020).

Fluconazole – OK to use in pregnancy?

Key messages

- Use of oral fluconazole during early pregnancy may increase the risk of spontaneous abortion.
- Doses higher than 150 mg during the first trimester may increase the risk of cardiac septal closure anomalies.
- Topical antifungals for the treatment of vaginal thrush remain an effective first-line therapy for most pregnant women.

Fluconazole is indicated for the treatment of fungal infections.¹ It is available on prescription and from a pharmacist as an oral single-dose treatment for vulvovaginal candidiasis (vaginal thrush).

In June 2020, the Medicines Adverse Reactions Committee (MARC) reviewed the data on fluconazole and its use in pregnancy.^{2,3} This review was triggered by the results of a study by Bérard et al which concluded that:

- any maternal exposure to fluconazole in early pregnancy may increase the risk of spontaneous abortion
- doses higher than 150 mg during the first trimester may increase the risk of cardiac septal closure anomalies in the fetus.⁴

Health care professionals are reminded that when treating vaginal thrush:³

- topical treatment remains an effective first-line therapy for most pregnant women
- questions around the possibility of pregnancy should be included in routine patient counselling.

References

1. Oakley A. 2003. *Fluconazole*. In: *DermNet NZ*. URL: dermnetnz.org/topics/fluconazole/ (accessed 15 September 2020).
2. Medsafe. 2020. *Medicines Adverse Reactions Committee: Fluconazole and use in pregnancy*. URL: medsafe.govt.nz/committees/MARC/reports/182-3.2.2Fluconazole.pdf (accessed 15 September 2020).
3. Medsafe. 2020. *Minutes of the 182nd Medicines Adverse Reactions Committee*. URL: medsafe.govt.nz/profs/adverse/Minutes182.htm#3.2.2 (accessed 15 September 2020).
4. Bérard A, Sheehy O, Zhao JP, et al. 2019. Associations between low- and high-dose oral fluconazole and pregnancy outcomes: 3 nested case-control studies. *Canadian Medical Association Journal* 191: E179–87. URL: ncbi.nlm.nih.gov/pmc/articles/PMC6379167/ (accessed 15 September 2020).

Test your knowledge: The *Prescriber Update* quiz 2020

Have you been reading *Prescriber Update* in 2020?

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 83 and the [Medsafe website](#).

1. When prescribing medicines for older patients, how can the anticholinergic burden be reduced?

- a) Avoiding, reducing or deprescribing medicines with anticholinergic activity
- b) Replace medicines with alternatives that do not have anticholinergic activity
- c) Start treatment at a low dose and increase slowly to the lowest effective dose
- d) All of the above

2. Oral zinc may increase the absorption of copper.

True False

3. A patient taking empagliflozin experiences nausea, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion and sleepiness. Their blood glucose is normal. What should you do?

4. If concomitant use of azathioprine and allopurinol is necessary, what should the azathioprine dose be reduced to?

- a) 10 percent of the recommended dose b) 25 percent of the recommended dose
- c) 75 percent of the recommended dose d) No dose reduction is necessary

5. Sweet syndrome:

- a) Is associated with medicines that reduce the production of white blood cells
- b) Is treated with antibiotics
- c) Only affects the eyes and mouth
- d) None of the above.

6. Patients with a deficiency of CYP2D6 may have [increased/reduced] effect from tramadol.

7. For patients who have undergone major gastrointestinal surgery, which of the following are recommended strategies which can be used to manage their medicines?

- a) Dose by weight
- b) Use extended release formulations
- c) Use medicines which can be monitored where possible
- d) Switch to a non-oral form of the medicine if available

8. Which of the following is a possible adverse reaction to long-term treatment with nitrofurantoin?

- a) Peripheral neuropathy b) Chronic interstitial lung disease
- c) Autoimmune-like hepatitis d) All of the above

9. Name two medicines associated with the development of fistulas.

10. Exposure to which synthetic progesterone may increase the risk of meningioma?

The Medsafe Files – Episode 14: Biosimilar medicines

Key messages

- A biosimilar is a biological medicine that is highly similar to another biological medicine that has already been approved in New Zealand.
- Medsafe applies the European Medicine Agency requirements when approving biosimilars for the New Zealand market.
- Biosimilars must meet international standards for quality, safety, and efficacy, as are used for all biological medicines.
- Biosimilars undergo extensive studies to demonstrate comparable pharmaceutical quality, safety, efficacy, and immunogenicity to their biological reference medicine.

Biosimilars are biological medicines that are highly similar to already approved biological medicines (the reference or innovator medicines). They are becoming increasingly common in clinical practice as more innovator biological medicines come off patent.

Characteristics of biological and biosimilar medicines

Biological medicines contain active ingredients that have been derived from a biological source, such as living cells and organisms. They are used for the treatment of a wide range of conditions such as diabetes, autoimmune diseases and cancers.¹

Typically, biological medicines contain a protein as the active ingredient, and the size and complexity of these proteins can vary greatly. The manufacturing process for biological medicines is usually more complex than that used for chemically-derived medicines and will often involve living cell systems and recombinant DNA technology.

Biological medicines are inherently variable

Biological sources demonstrate inherent variability when producing proteins. Not only do they produce the protein of interest, but they will produce it with minor variations, for example, small amounts of shortened proteins or proteins with different sugar molecules attached (glycosylation). When manufacturing biological medicines, this inherent variability is controlled within defined limits to ensure consistent safety and efficacy of the medicine. Therefore, batches of the same biological medicine can have minor differences even though they are manufactured using the same manufacturing process.

Biosimilars are highly similar but not identical to the reference medicine

Due to the inherent variability associated with biological medicines, along with the impact of using manufacturing processes that are specific to each manufacturer, minor differences can occur between the biosimilar and reference medicine. Consequently, a biosimilar medicine differs from a generic medicine in that the active ingredient is defined as being 'highly similar' rather than 'identical' to a reference medicine.

During the regulatory approval process, the biosimilar medicine must demonstrate that any minor differences to the reference medicine do not have any clinically meaningful impact on safety and efficacy. This is demonstrated in a clinical trial involving patients.

Approval of biosimilars in New Zealand

Medsafe uses the European Medicine Agency (EMA) regulatory requirements for approving biosimilar medicines because they have the most developed regulatory guidelines for biosimilars.¹

Biosimilars must meet international standards for quality, safety, and efficacy as are used for all biological medicines, although data requirements may vary. Equivalent pharmaceutical quality data requirements are applied to both the reference and biosimilar medicines, but the clinical data requirements for these medicines differ (see Table 1).

Table 1: Comparison of clinical data requirements for biological reference medicines and biosimilars

Biological reference medicine	Biosimilar medicine
<ul style="list-style-type: none">• Clinical trials demonstrate safety and efficacy in all claimed therapeutic indications.• Trials compare the reference medicine with a placebo or the current standard of therapy using defined endpoints• Trials performed in the intended patient population.	<ul style="list-style-type: none">• Clinical trials show clinical equivalence with the reference medicine.• Trial population may be healthy volunteers or patients, depending upon the toxicity of the medicine.• By demonstrating high similarity to the reference medicine, the biosimilar can mostly rely on the efficacy and safety information obtained for the reference medicine.

The data requirements for a biosimilar medicine rely on comparability studies with the reference medicine, including both quality and clinical comparability. The aim of the clinical comparability studies is to confirm that there are no differences between the two products that could affect efficacy and safety, including immunogenicity. If a biosimilar is shown to have comparable safety and efficacy to the reference medicine for one indication, the safety and efficacy data may be extrapolated to other indications. While this is the usual approach, extrapolation requires consideration of a number of factors including the mode of action of the biological medicine and its use across different clinical settings. Biological medicines are usually complex substances and their mode of action may involve multiple receptors or binding sites that may contribute differently to each indication. Also, in different clinical settings, safety and efficacy data for one indication (eg, rheumatoid arthritis) may not be directly applicable to an indication in another therapeutic area (eg, oncology) where the mode of action, dosage or pharmacokinetics may differ. In these situations, additional non-clinical or clinical studies may be required to prove the biosimilar is comparable to the reference medicine for the extrapolated indication.

Potential immunogenicity

Immunogenicity is the ability of proteins and other biological medicines to cause unwanted immune responses. Serious adverse reactions (eg, anaphylaxis) are considered rare. The more common immunogenicity response is the development of anti-drug antibodies (ADAs).¹ Many biological medicines are intended for long-term treatment of chronic conditions and the development of ADAs can negate the therapeutic effect of the biological medicine or reduce its efficacy.²

Clinical immunogenicity studies in patients are generally required for all biological medicines, including biosimilars. The immunogenicity studies provide data on the incidence, titre, and persistence of ADAs, assess the clinical impact and describe measures to manage the potential risk of immunogenicity (eg, special monitoring or use of concomitant medication to reduce infusion reactions).¹

Monitoring safety of biosimilars

Biosimilar medicines are monitored in New Zealand in the same way as other biological medicines, including the requirement for sponsors to submit periodic benefit risk evaluation reports (PBRERs) to Medsafe.^{3,4}

Please report suspected adverse reactions to a biosimilar medicine to the Centre for Adverse Reactions Monitoring (CARM). The brand and batch number should be included in this report.

More information

- **Medsafe position on biosimilars.**
- See the biosimilar medicine data sheets for specific prescribing information, including any monitoring requirements to manage the potential risk of immunogenicity (**search for data sheets on the Medsafe website**).
- **bpac^{NZ} has general information about prescribing biosimilars**, including planning for their introduction into clinical practice.
- **PHARMAC has information for patients about biosimilars.**

References

1. European Medicines Agency. 2019. *Biosimilars in the EU: Information Guide for Healthcare Professionals*. URL: ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf (accessed 27 July 2020).
2. Pratt, KP. 2018. Anti-drug antibodies: emerging approaches to predict, reduce or reverse biotherapeutic immunogenicity. *Antibodies* 7(2):19. DOI: 10.3390/antib7020019 (accessed 27 July 2020).
3. Medsafe. 2018. The Medsafe Files – Episode Five: Pharmacovigilance. *Prescriber Update* 39(1): 6–7. URL: msd.govt.nz/profs/PUArticles/March2018/msd-files-pharmacovigilance.htm (accessed 24 September 2020).
4. Medsafe. 2020. *Guideline on the Regulation of Therapeutic Products in New Zealand: Part 8: Pharmacovigilance* (Edition 2.2). URL: msd.govt.nz/regulatory/Guideline/GRTPNZ/part-8-pharmacovigilance.pdf (accessed 24 September 2020)

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
Bupropion	Possible risk of psoriasis exacerbation	29 March 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.

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
6/11/2020	Alert	Update to Original Communication – Important updates to clozapine data sheets and monitoring during covid-19 pandemic
5/11/2020	Notices	Codeine-containing medicines have now been reclassified
3/11/2020	Notices	Notice of Medsafe Office Closure Christmas/New Year 2020/2021
30/10/2020	Monitoring	UPDATE: Concern reported with the use of NovoRapid® Penfill® (insulin aspart; 3 mL cartridge) by type 1 diabetes patients
23/10/2020	Monitoring	Concern reported with the use of NovoRapid® Penfill® (insulin aspart; 3 mL cartridge) by type 1 diabetes patients
22/10/2020	Media release	Codeine-containing medicines to be reclassified
19/10/2020	Notices	Influenza Vaccine Composition – 2021
1/10/2020	Dear Healthcare Professional Letter	Norimin 28 Day/Brevinor-1 28 Day – temporary disruption to product supply (PDF, 1 page, 58 KB)
29/09/2020	Monitoring	 Possible risk of psoriasis exacerbation with bupropion
23/09/2020	Consultation	Outcome of the consultation on the proposed warning statements for substances (eg, allergens) in medicines that may cause undesirable reactions
16/09/2020	Alert	Medsafe is issuing a warning that Elevacity Elevate Smart Coffee (Version 3) should not be consumed – statement under section 98 of the Medicines Act 1981
15/09/2020	Media release	Medsafe takes action to prevent the supply of illegally marketed medicine linked to liver harm
4/09/2020	Dear Healthcare Professional Letter	Setrona – Supply of Australian-labelled Setrona 50 mg and 100 mg tablets in New Zealand (PDF, 2 pages, 757 KB)
03/09/2020	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
18/08/2020	Dear Healthcare Professional Letter	Brevinor 28 Day (Australian stock) – Temporary alternative product supply to cover Norimin stock shortage (PDF, 1 page, 158 KB)

Gathering knowledge from adverse reaction reports: December 2020

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

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

Case details ^{a,b}	Reaction description and data sheet information ^{b,c}
CARM ID: 136929 Age: 70 Gender: Female Medicine(s): Chloramphenicol Reaction(s): Aplastic anaemia	<p>Following cataract surgery, the patient administered chloramphenicol eye drops for one week. Some months later, she developed fatal aplastic anaemia.</p> <p>The Chlorafast data sheet includes a warning that aplastic anaemia and death have been rarely reported following local application of chloramphenicol. It states that chloramphenicol should not be used when less potentially dangerous agents would be expected to provide effective treatment.</p> <p>See also the <i>Prescriber Update</i> article, 'A drop in the eye has widespread ripples'.</p>
CARM ID: 137204 Age: 35 Gender: Female Medicine(s): Zopiclone, sertraline Reaction(s): Abnormal behaviour, delusion, euphoric mood, mania, nightmare	<p>A patient on long-term sertraline was prescribed zopiclone. Shortly after taking the first dose, she experienced euphoria, mania, abnormal behaviour, delusion and nightmares.</p> <p>The Zopiclone Actavis data sheet lists abnormal behaviour, delusion, euphoria and nightmares as possible adverse reactions. The Setrona data sheet also lists euphoric mood, mania and nightmares.</p>
CARM ID: 137272 Age: 32 Gender: Female Medicine(s): Nifedipine Reaction(s): Product problem	<p>A patient taking controlled release nifedipine noticed a pink pill in her stools a few times. The pills appeared to be intact, except that the coating was worn off in one spot.</p> <p>The Adalat Oros modified release tablet has a pink coat with a small laser hole on one side. Section 5.2 of the data sheet states that, upon swallowing, the biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the faeces as an insoluble shell.</p> <p>See also the <i>Prescriber Update</i> article, 'Ghosts of medicines passed'.</p>
CARM ID: 137729 Age: 60 Gender: Female Medicine(s): Hydroxychloroquine Reaction(s): QT prolongation	<p>A patient taking hydroxychloroquine experienced cardiac dysrhythmia. An ECG showed an elongated QT interval.</p> <p>The Plaquenil data sheet includes a warning for QT prolongation, and states that hydroxychloroquine has the potential to prolong the QTc interval in patients with specific risk factors, such as advanced age, uncorrected hypokalaemia and/or hypomagnesaemia, cardiac disease or treatment with other QT interval prolonging agents.</p>

CARM ID: 137798 Age: 83 Gender: Female Medicine(s): Omeprazole Reaction(s): Metabolic acidosis, lethargy, nausea, renal impairment, tubulointerstitial nephritis	<p>Within days of starting omeprazole, the patient felt unwell, lethargic, nauseated and short of breath. Upon admission to hospital she was found to have an acute kidney injury with metabolic acidosis – likely due to interstitial nephritis.</p> <p>Interstitial nephritis is listed as a rare adverse reaction in the Omeprazole Actavis data sheet.</p>
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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).

Dissecting systemic VEGF inhibitors: effects on arteries

Key messages

- Systemic vascular endothelial growth factor (VEGF) inhibitors increase the risk of aneurysms and artery dissections.
- Regularly monitor blood pressure during treatment with VEGF inhibitors. Refer smokers to a smoking cessation service.

Background

Recently, an association between the use of vascular endothelial growth factor (VEGF) inhibitors and aneurysms and artery dissections has been identified. However, no cases have been reported in New Zealand to date.

VEGF inhibitors

Systemic VEGF inhibitors are used to treat a variety of cancers. VEGF inhibitors are thought to inhibit tumour growth by:¹

- preventing endothelial cell proliferation and depriving the tumour vascular supply
- improving chemotherapy delivery by normalising tumour vasculature.

Table 1 shows the currently approved systemic VEGF inhibitors in New Zealand.

Table 1: Approved systemic VEGF inhibitors in New Zealand

Active substance	Brand name
Axitinib	Inlyta
Nintedanib	Ofev
Bevacizumab	Avastin
Pazopanib	Votrient
Regorafenib	Stivarga
Sorafenib	Nexavar
Sunitinib	Sutent
Tivozanib	Fotivda

Source: Medsafe Product/Application search. URL: medsafe.govt.nz/regulatory/dbsearch.asp (accessed 24 September 2020).

Aneurysm and artery dissection

An aneurysm is a ballooning of a weakened area in a blood vessel. Aneurysms may rupture, resulting in internal bleeding.

An artery dissection is a tear in the artery lining. As the tear becomes larger, it forms a pouch where blood can accumulate. This can cause blood clots or block the flow of blood.²

Hypertension, smoking and high cholesterol are modifiable risk factors for aneurysms and artery dissections.³ Managing these risk factors can lower the risk of occurrence. Non-modifiable risk factors include increasing age and a family history of aneurysm and artery dissection.³

The mechanism by which VEGF inhibitors can cause aneurysms and artery dissection is unclear but may include aggravation of pre-existing hypertension and/or changes in the structure of the vascular endothelium.^{3,4}

Interestingly, aneurysms and artery dissections have also been reported in patients taking VEGF inhibitors without hypertension.^{3,4}

Minimising the risk

To minimise the risk of aneurysms and artery dissections in patients treated with VEGF inhibitors:

- regularly monitor blood pressure during treatment. Antihypertensive therapies should be initiated or adjusted according to blood pressure treatment guidelines⁵
- refer smokers to a smoking cessation service.³

References

1. Kuo CJ. 2020. Overview of angiogenesis inhibitors. In: *UpToDate* 14 May 2020. URL: uptodate.com/contents/overview-of-angiogenesis-inhibitors (accessed 24 September 2020).
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Recent approvals: new active ingredients or new indications

For the period 16 July 2020 to 15 October 2020.

Recent approvals of medicines with new active ingredients

Trade name (active ingredient)	Dose form and strength(s)	Therapeutic area
Cabometyx (cabozantinib)	Tablet 20 mg 40 mg 60 mg	Renal cell carcinoma
Carglumic Acid Waymade (carglumic acid)	Tablet 200 mg	Hyperammonaemia
Emgality (galcanezumab)	Solution for injection 120 mg/mL prefilled pen 120 mg/mL prefilled syringe	Migraine
Faslodex (fulvestrant)	Solution for injection 250 mg/5 mL	Breast cancer
Fycompa (perampanel)	Tablet 2 mg 4 mg 6 mg 8 mg 10 mg 12 mg	Epilepsy
Monofer (ferric derisomaltose)	Solution for injection 100 mg/mL 200 mg/2 mL 500 mg/5 mL 1000 mg/10 mL	Iron deficiency
Prevymis (letermovir)	Tablet 240 mg 480 mg Concentrate for infusion 240 mg/12 mL 480 mg/24 mL	Cytomegalovirus infection

Approved medicines with new indications

Trade Name (active ingredient)	Dose form and strength(s)	New therapeutic area(s)
Forxiga (dapagliflozin)	Tablet 10 mg	Heart failure (in both diabetic and non-diabetic patients)
Imfinzi (durvalumab)	Concentrate for infusion 120 mg/2.4 mL 500 mg/10 mL	Small cell lung cancer
Lucentis (ranibizumab)	Solution for injection 10 mg/mL	Diabetic retinopathy
Soliris (eculizumab)	Solution for infusion 300 mg/30 mL	Haemolytic uraemic syndrome
Spravato (esketamine)	Nasal solution 140 mg/mL	Major depressive disorder
Tecentriq (atezolizumab)	Concentrate for infusion 1200 mg/20 mL	Hepatocellular carcinoma
Venclexta (venetoclax)	Tablet 10 mg 50 mg 100 mg 10 mg, 50 mg, 100 mg combination pack	Acute myeloid leukaemia

- See the Medsafe website for [more information about these medicines](#).
- [Data sheets of currently marketed medicines](#) are also available.

A bitter-Sweet syndrome with potential autoimmune connections

Key messages

- Sweet syndrome is a rare skin condition characterised by fever and sudden onset of painful skin lesions.
- In rare cases, Sweet syndrome has been reported to occur in association with Sjögren's syndrome, an autoimmune condition characterised by dry eyes and mouth.

Background

A 51-year-old woman developed fever, arthralgia and a general painful macular rash a few days after influenza vaccination. The case was reported to the Centre for Adverse Reactions Monitoring (CARM ID 137192). A skin biopsy confirmed a diagnosis of Sweet syndrome. The case report also stated the patient had presumed Sjögren's syndrome.

This article describes Sweet syndrome and how it may be connected to Sjögren's syndrome.

Sweet syndrome

Sweet syndrome (acute febrile neutrophilic dermatosis) is a rare skin condition, characterised by fever and sudden onset of painful skin lesions that appear mostly on the limbs and neck.^{1,2} Mucosal surfaces such as the eyes and mouth may also be involved.²

Sweet syndrome belongs to a heterogenic group of neutrophilic dermatoses³, with neutrophils accumulating in the dermis or in the fatty layer of tissue just below the skin.³ It was first described by Dr Robert Douglas Sweet in 1964.²

The cause of Sweet syndrome is often unknown. However, there are three subtypes based on aetiology: classical or idiopathic, malignancy-associated, and drug-induced.⁴

- Classical or idiopathic Sweet syndrome: the disorder occurs by itself for no known reason. Some people experience an upper respiratory infection, gastrointestinal infection, or influenza-like illness that precedes their skin lesions by one to three weeks.³
- Malignancy-associated Sweet syndrome: associated with certain types of cancer, such as leukaemia.³
- Drug-induced Sweet syndrome: including granulocyte-colony stimulating factor (G-CSF), azathioprine, All-trans retinoic acid (ATRA) and, with less evidence, vaccination, anticancer agents, trimethoprim + sulphamethoxazole and other antibiotics, nonsteroidal anti-inflammatory medicines and hydroxychloroquine.^{5,6}

Sweet syndrome is usually treated with corticosteroids. The treatment usually results in rapid improvement of symptoms, but lower doses may be required for several weeks to months to prevent reoccurrence of symptoms.²

Sjögren's syndrome

Sjögren's syndrome is an autoimmune condition that may develop either as a primary disease or as a secondary complication of another autoimmune disease, such as rheumatoid arthritis or lupus. It most commonly affects older women. The main symptoms are dry mouth and eyes but other parts of the body, such as joints and kidneys, may also be affected.⁷

Treatment is primarily symptomatic. Artificial tears are used for dry eyes, and dry mouth may be relieved by saliva substitutes or medicines that stimulate saliva flow such as pilocarpine. All patients must receive regular dental care to prevent cavities and tooth loss.⁷ Hydroxychloroquine is also used for treatment of Sjögren's syndrome.

Is Sweet syndrome associated with vaccination or Sjögren's syndrome?

The patient in the CARM case report developed Sweet syndrome after influenza vaccination. A few cases of Sweet syndrome after vaccination have been described in the literature.⁵ One woman developed Sweet syndrome 12 hours after influenza vaccination.⁸

The patient in the case reported to CARM had also previously been diagnosed with Sjögren's syndrome. Sweet syndrome has been associated with a multitude of conditions, including Sjögren's syndrome, but the evidence for an association has been very weak^{5,6}. A literature review including articles up to October 2019 only found six publications where Sweet syndrome had occurred in patients with secondary Sjögren's syndrome, and one publication where a patient with primary Sjögren's syndrome developed Sweet syndrome.⁶

Four cases of Sweet syndrome have been reported to CARM. The case mentioned above is the only one that reports both Sweet and Sjögren's syndromes. Six other cases have been reported where Sjögren's syndrome is listed as either a reaction or a possible pre-existing condition. Data is very limited in all of these CARM reports.

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Acute generalised exanthematous pustulosis (AGEP)

Key messages

- Acute generalised exanthematous pustulosis (AGEP) is a type IV (T-cell mediated) hypersensitivity reaction.
- Over 90 percent of cases of AGEP are caused by medicines, most commonly antibiotics.
- AGEP typically resolves spontaneously following withdrawal of the causative medicine.
- Patients should avoid re-exposure to the causative medicine following AGEP.

What is AGEP?

Acute generalised exanthematous pustulosis (AGEP) is a rare type of severe cutaneous adverse reaction (SCAR).^{1,2} Like other SCARs, such as Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), AGEP is a type IV (T-cell mediated) hypersensitivity reaction.^{1–3} The T-cell mediated response in AGEP results in neutrophilic inflammation,^{1,2} but there can be some overlap between the different types of SCAR and patients may have clinical features of SJS/TEN or DRESS with AGEP.^{2–4}

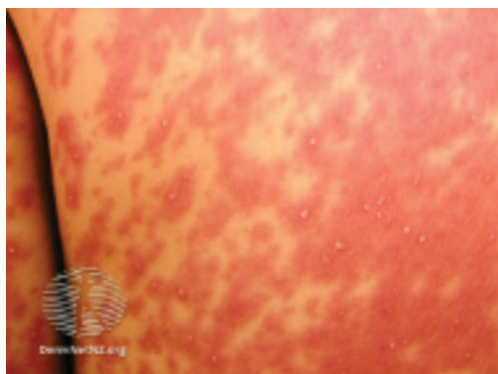
How does AGEP present?

AGEP is characterised by the rapid appearance of sterile, non-follicular, pin-head sized pustules on an erythematous base (Figure 1), typically starting on the face and skin flexures before becoming more widespread.^{4,5} Over 90 percent of cases of AGEP are provoked by medicines.⁴ The rash usually develops rapidly, within two days of exposure to the offending medicine,^{2,4} but onset may occur up to two weeks after initial exposure to some medicines.^{2,3}

In the acute phase, patients may have a fever above 38°C and an elevated neutrophil count,^{2,5,6} but internal organ involvement is uncommon.^{2,4}

Most patients recover from AGEP within 10–14 days of withdrawal of the causative medicine.^{1,4–7} The pustular eruptions desquamate during the recovery phase.^{2,6} The mortality rate from AGEP is approximately 2–4 percent.^{1,3}

Figure 1: Patient with acute generalised exanthematous pustulosis (AGEP), showing pinpoint pustules on an erythematous base



Source: DermNet NZ. URL: dermnetnz.org/imagetaital/3457?copyright=&label= (accessed 21 October 2020). No changes were made to this watermarked image. Creative Commons Attribution-NonCommercial-NoDerivs 3.0 (New Zealand). URL: creativecommons.org/licenses/by-nc-nd/3.0/nz/legalcode.

How is AGEP managed?

Treatment primarily involves withdrawal of the causative medicine. Supportive care in hospital (including fluid and electrolyte replacement) is often required during the acute illness.^{2,4} Moisturisers, topical corticosteroids, oral antihistamines and analgesics may be required for symptomatic relief.^{2,4} Systemic corticosteroids may be used to control inflammation in the acute phase.²

Patients with AGEP should avoid re-exposure to the causative medicine.²

Which medicines are associated with AGEP?

Antibiotics are among the most commonly implicated medicines. Other medicines associated with AGEP include oral antifungals (eg, terbinafine), calcium channel blockers (eg, diltiazem), hydroxychloroquine, carbamazepine and paracetamol.⁴ Ibuprofen has recently been highlighted as a causative agent for AGEP.⁸

As at 1 October 2020, the Centre for Adverse Reactions Monitoring (CARM) has received 25 reports of AGEP, of which five reports included more than one suspect medicine. The reported medicines are shown in Table 1.

Table 1: Medicines reported in association with acute generalised exanthematous pustulosis (AGEP), December 2000 to October 2020

Suspect medicine	No. of reports
Antibiotics:	
Penicillins	5
Cephalosporins	2
Clindamycin	2
Tetracyclines	2
Co-trimoxazole	2
Trimethoprim	1
Ciprofloxacin	1
Terbinafine	3
Hydroxychloroquine	3
Diltiazem	3
Contrast media	2
Other:	
Allopurinol	1
Bendamustine	1
Ibuprofen	1
Ondansetron	1
Rituximab	1

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Quiz answers

1. **d.** To reduce the anticholinergic burden in older patients, avoid, reduce, or deprescribe medicines with anticholinergic activity; replace certain medicines with alternatives that do not have anticholinergic properties; start treatment at a low dose and increase slowly to the lowest effective dose. (June 2020)
2. **False.** Oral zinc may inhibit the absorption of copper, leading to reduced copper levels, and potentially copper deficiency. (March 2020)
3. These symptoms may be due to diabetic ketoacidosis (DKA). If DKA is suspected, discontinue treatment with empagliflozin, evaluate the patient and initiate treatment. (December 2020)
4. **b.** Concomitant use of allopurinol and azathioprine is not recommended. However, if co-administration is necessary, reduce the dose of azathioprine to 25 percent of the recommended dose and closely monitor the patient's blood count. (September 2020)
5. **d.** None of the above. Sweet syndrome is associated with medicines that increase production of white blood cells; is treated with corticosteroids; skin lesions appear mostly on the limbs and neck. (December 2020)
6. Patients with a deficiency of CYP2D6 may have reduced effect from tramadol. (June 2020)
7. **a, c and d.** Extended release formulations should be avoided. (September 2020)
8. **d.** Peripheral neuropathy, interstitial lung disease and hepatitis are all possible adverse reactions to long-term nitrofurantoin treatment. (March 2020)
9. Any two of the following: axitinib, bevacizumab, nicorandil, pazopanib, tocilizumab. (June 2020)
- 10 Cyproterone acetate. (September 2020)

Medsafe

New Zealand Medicines and Medical Devices Safety Authority

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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

Lily Chan, Principal Technical Specialist Pharmacovigilance

Maria Storey, Senior Advisor Pharmacovigilance

Nevin Zhong, Advisor Pharmacovigilance

Nina Kyle, Principal Technical Specialist Medicines Assessment

Dr Susan Kenyon, PhD, Manager Clinical Risk

Tegan Coventry, Advisor Pharmacovigilance

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Clinical Advisor Dr Tina Ireland

Group Manager Chris James

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