Prescriber Update

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Contents

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MINISTRY OF HEALTH

Reminder: Flozins and the risks of diabetic ketoacidosis and Fournier's gangrene

Key messages

- Sodium-glucose co-transporter 2 (SGLT-2) inhibitors (or 'flozins') are used in the treatment of type 2 diabetes mellitus and heart failure. Empagliflozin and dapagliflozin are the SGLT-2 inhibitors approved in New Zealand.
- Patients taking SGLT-2 inhibitors are at increased risk of diabetic ketoacidosis and Fournier's gangrene.
- Inform patients taking SGLT-2 inhibitors about these serious and life-threatening conditions, including the signs and symptoms and when to seek medical attention.

Introduction

The Centre for Adverse Reactions Monitoring (CARM) has received reports of diabetic ketoacidosis (DKA) and Fournier's gangrene (FG) in patients taking empagliflozin. Medsafe is reminding health professionals about the risk of these serious and sometimes life-threatening conditions in patients taking sodium-glucose co-transporter 2 (SGLT-2) inhibitors.[1,2]

Empagliflozin and dapagliflozin are SGLT-2 inhibitors indicated for the treatment of type 2 diabetes mellitus and heart failure.[1,2] Both medicines are available as single-substance formulations (Jardiance, Forxiga) or in combination with metformin (Jardiamet, Xigduo XR). In addition to improving glycaemic control in patients with type 2 diabetes, SGLT-2 inhibitors slow kidney function decline and reduce the risk of cardiovascular death and hospitalisation in patients with heart failure.[1,2]

Medsafe has requested updates to the empagliflozin and dapagliflozin data sheets.

The benefits of SGLT-2 inhibitors continue to outweigh the risks of harm.

Patients taking SGLT-2 inhibitors are at increased risk of diabetic ketoacidosis

DKA is a complication of diabetes and develops when insulin levels are insufficient to meet the body's metabolic requirements.[3] It is more common in patients with type 1 diabetes, but DKA can occur in patients with type 2 diabetes.[3]

DKA has also been reported as a rare adverse reaction to SGLT-2 inhibitors.[1,2] Individuals with SGLT-2 inhibitor-associated DKA may have normal or mildly elevated blood glucose (euglycaemic DKA).[4]

Advise patients to seek medical attention immediately if they are experiencing signs and symptoms of DKA, regardless of their blood glucose level.[4] Symptoms may include nausea, vomiting, excessive thirst, abdominal pain and difficulty breathing.[4]

Discontinue SGLT-2 inhibitor treatment if DKA is suspected and follow local protocols for DKA treatment.[4] If the patient developed DKA while taking an SGLT-2 inhibitor, do not restart treatment unless another clear precipitating factor is identified and resolved.[5]

Interrupt treatment with SGLT-2 inhibitors if patients have diabetic ketoacidosis risk factors

Factors that increase the risk of DKA in patients taking SGLT-2 inhibitors include a low carbohydrate diet, dehydration, acute illness, surgery, insulin deficiency from any cause, reduced caloric intake or increased insulin requirements.[5]

If patients taking SGLT-2 inhibitors also have DKA risk factors, consider monitoring for DKA and temporarily discontinuing treatment. Consider ketone monitoring, even if treatment has been interrupted, and follow local protocols.[5]

Interrupt treatment with SGLT-2 inhibitors in patients who are hospitalised for major surgical procedures.[5,6] During this time, patients may require increased doses of other glucose-lowering agents, plus ketone monitoring.[5-7] Restart treatment with SGLT-2 inhibitors only when the ketone values are normal, and the patient's condition has stabilised.[7]

Fournier's gangrene and SGLT-2 inhibitors

FG is a rapidly progressive infection of the deep soft tissues, affecting the fascia planes in the perineal, perianal or genital areas. FG is also known as 'necrotising fasciitis of the perineum and genitalia'.[8]

SGLT-2 inhibitors lower blood glucose by inhibiting glucose reabsorption in the renal tubule.[1,2] Subsequent glycosuria (glucose in the urine) can favour the growth of microorganisms,[8] increasing the risk of urinary tract infections.[5]

Residual bacteria from ineffective cleaning of the anogenital area, coupled with high glucose content of the urine, can promote both urinary tract infections and localised infections. If the infection is not appropriately treated, the bacteria may infect the deeper soft tissues by breaching mucosal barriers or a break in the skin. Infection of these deep soft tissues may then progress to FG.[8]

Diabetes and SGLT-2 inhibitors are risk factors for Fournier's gangrene

FG typically affects males, but cases have been reported in females. Patients with comorbidities that affect cellular immunity or microcirculation are at increased risk of FG. Patients with diabetes are also at increased risk of FG, with diabetes present in 60% of FG cases.[8]

FG has also been reported with SGLT-2 inhibitors.[1,8] Patients treated with SGLT-2 inhibitors who present with pain or tenderness, erythema, swelling in the genital or perineal area, fever or malaise should be evaluated promptly for FG.[1]

Discontinue SGLT-2 inhibitor treatment immediately if FG is suspected.[1]

Advise patients to watch out for Fournier's gangrene

Advise patients to check the genital area regularly for signs or symptoms of FG and seek medical attention immediately if symptoms occur.[7,9] Encourage patients to maintain good genital hygiene.[9]

Consider managing other FG risk factors, such as smoking and obesity, and maintaining diabetes control.[10]

Medsafe recently published a consumer information leaflet (PDF, 248 KB, 2 pages) with information for patients about FG.

New Zealand case reports

As of 30 September 2022, CARM had received a total of 24 reports of DKA with empagliflozin. Of these, 22 reports were for empagliflozin, and 2 were for empagliflozin + metformin. The reports indicate that DKA can happen at any point during treatment. Euglycemic DKA was reported in several cases.

As of 30 September 2022, CARM had received a total of 6 reports of Fournier's gangrene with empagliflozin. Of these reports, 4 were in males and 2 in females.

More information

See the sponsors' data sheets and consumer medicine information (CMI) leaflets published on the Medsafe website.

- Search for a data sheet or CMI

For prescribers

- *Prescriber Update* December 2020: Spotlight on empagliflozin
- *Prescriber Update* September 2021: Empagliflozin: advise patients on the risk of ketoacidosis and Fournier's gangrene

For patients

- Medsafe consumer information leaflet: Watch out for Fournier's gangrene (infection) when taking SGLT2 inhibitors like empagliflozin (PDF, 248 KB, 2 pages)
- Health Navigator medicine information: Empagliflozin

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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
3/11/2022	Dear Healthcare Professional Letter	Imbruvica (ibrutinib) – data sheet updates to dose modifications for adverse reactions and to warnings and precautions (PDF, 3 pages, 333 KB)
2/11/2022	Committees	Reclassification of choline salicylate
8/09/2022	Alert	Myocarditis and pericarditis have been reported with Nuvaxovid (Novavax COVID-19 Vaccine)
5/09/2022	Alert	Recall of KetoSens Test Strips – batch UJ03PBXNG

Adverse drug reactions reported following use of oral COVID-19 therapeutics in New Zealand

Key messages

- Nirmatrelvir + ritonavir (Paxlovid) and molnupiravir (Lagevrio) are new oral antiviral medicines for treatment of COVID-19 infection.
- Please report suspected adverse drug reactions for these new medicines to the Centre for Adverse Reactions Monitoring (CARM) so that Medsafe and CARM can closely monitor their safety.
- Paxlovid is a cytochrome P450 3A (CYP3A) inhibitor with the potential for many drug-drug interactions. Be aware of these interactions before prescribing Paxlovid and take an up-to-date medication history. Advise patients to check with their healthcare professional before starting new medicines or herbal products.

This article provides an overview of suspected adverse drug reactions (ADRs) to nirmatrelvir + ritonavir (Paxlovid) and molnupiravir (Lagevrio) reported to the Centre for Adverse Reactions Monitoring (CARM).

Paxlovid and Lagevrio are oral antiviral treatments for COVID-19 infection, given provisional approval on 2 March 2022 and 14 April 2022, respectively.

It is important to report suspected ADRs for these new medicines to CARM so that Medsafe and CARM can closely monitor their safety and identify new safety concerns. Reporting is easiest online.

Paxlovid

As of 30 September 2022, CARM had received a total of 72 reports where Paxlovid was listed as the suspect or interacting medicine. Table 1 provides an overview of suspected ADRs reported following the use of Paxlovid.

Table 1: Overview of suspected adverse drug reactions following the use of Paxlovid (nirmatrelvir + ritonavir) reported to the Centre for Adverse Reactions Monitoring as of 30 September 2022 (list not exhaustive[a]), and relevant data sheet text

Adverse drug reaction	Number of reports	What the Paxlovid data sheet says[b,c]
Taste disturbances	17	Dysgeusia: reported as a common adverse event in clinical trials
Diarrhoea	14	Diarrhoea: reported as a common adverse event in clinical trials
Nausea	12	Nausea: identified as an adverse event during post-marketing use of Paxlovid
COVID-19 rebound effect	11	Post-treatment increases in SARS-CoV-2 nasal RNA levels (ie, viral RNA rebound) were observed on day 10 and/or day 14 in a subset of Paxlovid and placebo recipients in clinical trials, irrespective of COVID-19 symptoms.
Vomiting	9	Vomiting: reported as a common adverse event in clinical trials
Hypertension	3	Hypertension: reported as an uncommon adverse event in clinical trials
Jaundice	2	The warnings and precautions/hepatotoxicity section states that jaundice has occurred in patients receiving ritonavir. Caution should be exercised in patients with pre-existing liver diseases, liver enzyme abnormalities or hepatitis.

Notes:

a. Reports can include more than one suspected ADR. Not all reported ADRs are shown in the table.

b. Pfizer New Zealand Limited. 2022. *Paxlovid New Zealand Data Sheet* 15 September 2022. URL: medsafe.govt.nz/profs/Datasheet/p/paxlovidtab.pdf (accessed 18 October 2022).

c. Frequencies are defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); not known (frequency cannot be estimated from the available data).

Potential drug-drug interactions with Paxlovid

Paxlovid is a cytochrome P450 3A (CYP3A) inhibitor and may increase plasma concentrations of medicines primarily metabolised by this enzyme.[1] Patients taking Paxlovid may be more susceptible to ADRs from their usual medicines if potential drug-drug interactions are not appropriately managed.

To minimise the risk of drug-drug interactions:

- refer to the data sheet and other available resources to screen and manage these interactions before prescribing and dispensing Paxlovid
- take an up-to-date medication history, including regular prescription medicines, medicines taken as needed, over-the-counter (OTC) medicines and any herbal products
- advise patients taking Paxlovid to check with their healthcare professional before starting any new medicines (prescription or OTC) and herbal products.

Table 2 lists some medicines and herbal products contraindicated for concomitant use with Paxlovid.

Table 2: Medicines and herbal products that are contraindicated for concomitant use with Paxlovid* (nirmatrelvir + ritonavir)

Interactions that result in an increase or decrease in concentrations of concomitant medicine and are associated with serious and/or life-threatening reactions	
Medicinal product class	**Medicinal products within the class**
Antianginal	Ranolazine
Antiarrhythmics	Amiodarone, flecainide, propafenone
Antibiotic	Fusidic acid
Anticancer	Neratinib, venetoclax
Anti-gout	Colchicine
Antipsychotics	Clozapine
Ergot derivatives	Ergometrine
HMG-CoA reductase inhibitors	Simvastatin
Opioid analgesic	Pethidine
PDE5 inhibitor	Avanafil, sildenafil, vardenafil, tadalafil
Sedative/hypnotics	Diazepam, triazolam
Interactions that result in a decrease in Paxlovid concentrations and are associated with loss of virologic response and possible resistance	
Product class	**Products within the class**
Anticancer	Apalutamide
Anticonvulsant	Carbamazepine, phenobarbital, phenytoin
Antimycobacterials	Rifampicin
Herbal products	St. John's Wort (*Hypericum perforatum*)

* Medicines listed in this table are a guide and are not considered a comprehensive list of all possible medicines that may be contraindicated with Paxlovid.

Source: Pfizer New Zealand Limited. 2022. *Paxlovid New Zealand Data Sheet* 15 September 2022. URL: medsafe.govt.nz/profs/Datasheet/p/paxlovidtab.pdf (accessed 18 October 2022).

Lagevrio

As of 30 September 2022, CARM had received a total of 11 reports where Lagevrio was listed as the suspect medicine. Table 3 provides an overview of suspected ADRs reported following the use of Lagevrio.

Table 3: Overview of suspected adverse drug reactions following the use of Lagevrio (molnupiravir) reported to the Centre for Adverse Reactions Monitoring as of 30 September 2022 (list not exhaustive[a]), and relevant data sheet text

Adverse drug reaction	Number of reports	What the Lagevrio data sheet says[b]
Skin reactions	6	Erythema, rash and urticaria: identified as adverse reactions during post-marketing use of Lagevrio
Nausea	2	Nausea: reported in 1% of participants taking Lagevrio and placebo in clinical trials
Vomiting	2	Vomiting: reported in 1% of participants taking Lagevrio and placebo in clinical trials
Diarrhoea	2	Diarrhoea: reported in 2% of participants taking Lagevrio and placebo in clinical trials

Notes:

a. Reports can include more than one suspected ADR. Not all reported ADRs are shown in the table.

b. Merck Sharp & Dohme (New Zealand) Limited. 2022. *Lagevrio New Zealand Data Sheet* 14 April 2022. URL: medsafe.govt.nz/profs/datasheet/l/lagevirocap.pdf (accessed 18 October 2022).

More information

- How Medsafe monitors the safety of medicines
- See the medicine's data sheet and Consumer Medicine Information for the known side effects
- Search the Suspected Medicine Adverse Reaction Search (SMARS) database for reports of suspected adverse drug reactions to medicines
- Ministry of Health: COVID-19: Advice for all health professionals

Reference

1. Pfizer New Zealand Limited. 2022. *Paxlovid New Zealand Data Sheet.* 15 September 2022. URL: medsafe.govt.nz/profs/Datasheet/p/paxlovidtab.pdf (accessed 18 October 2022).

We need your help!

MEDICINES MONITORING

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

Medicine(s)	Potential safety issue	Active monitoring ends
Oral anticoagulants	Abnormal uterine bleeding	28 February 2023

- 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.

Test your knowledge: The *Prescriber Update* quiz 2022

Have you been reading *Prescriber Update* in 2022?
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 66 and the **Medsafe website**.

1. Non-steroidal autoinflammatory drugs (NSAIDs) are contraindicated during which trimester of pregnancy?
2. Trimethoprim or _____ can interact with methotrexate to cause bone marrow suppression.
3. List 3 factors that increase the risk of diabetic ketoacidosis in patients taking a sodium-glucose co-transporter 2 (SGLT-2) inhibitor.
4. Systemic ciprofloxacin may [increase/decrease] the serum concentration of levothyroxine.
5. Consider drug–drug interactions with Paxlovid (nirmatrelvir + ritonavir) due to its inhibitory effects on:
   a. CYP3A b. CYP2D6 c. CYP2C9 d. CYP1A2
6. Patients taking bimatoprost who have mild enophthalmos, orbital fat atrophy and/or inferior scleral show may be experiencing which condition?
7. In patients taking combined oral contraceptives (COCs), when is the risk of venous thromboembolism (VTE) the highest?
8. List 3 opioid medicines that are high-risk for inducing serotonin syndrome when used with serotonergic medicines.
9. Which of the following are suggested mechanisms whereby vitamin E may cause bleeding:
   a. Scavenging of free radicals
   b. Inhibition of platelet aggregation
   c. Tocopheryl quinone has anticoagulant activity
   d. Alpha-tocopherol can interfere with vitamin K metabolism
10. True or False: St John's Wort can reduce the clinical effects of warfarin.

MARC's remarks: September 2022 meeting

The Medicines Adverse Reactions Committee (MARC) convened on 8 September 2022.

The Committee reviewed the risk of major adverse cardiovascular events (MACE), malignancies and thromboembolism as separate events with **Janus kinase (JAK) inhibitors (tofacitinib, upadacitinib** and **ruxolitinib)**. The Committee considered that the risk of each event would be influenced by underlying risk factors in an individual and this should be considered when considering the benefit–risk for use in the individual. The Committee noted that there was currently insufficient data to distinguish whether the safety concerns differ between the medicines of the class. Therefore, the safety concerns should be treated as a class effect until further evidence is available. The Committee recommended strengthening the warning statements for MACE, malignancies and thromboembolic events in the tofacitinib and upadacitinib data sheets. The same warning statements should also be added to the ruxolitinib data sheet.

A potential drug-drug interaction between **cannabidiol** and **systemic mammalian target of rapamycin (mTOR) (tacrolimus, cyclosporin)** and **calcineurin inhibitors (sirolimus, everolimus)** was discussed. The Committee noted that cannabidiol likely has a wide effect on cytochrome P450 enzymes and transporters, however, this is not yet fully understood. The Committee agreed that the evidence showed a clinically significant drug interaction between cannabidiol and mTOR and recommended updates to sirolimus data sheet.

The Committee discussed **quetiapine** and the risk of gestational diabetes (GDM). The Committee considered that due to metabolic adverse effects, quetiapine can increase the risk of GDM. Data sheet updates were recommended.

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

Microscopic colitis – could it be caused by a medicine?

Key messages

- Microscopic colitis causes chronic, watery, non-bloody diarrhoea.
- Consider medicines as a possible cause of microscopic colitis.

Microscopic colitis

Microscopic colitis is an inflammatory disease of the colon that causes chronic, watery, non-bloody diarrhoea.[1] Patients often experience between 4 and 9 watery stools per day, but in rare cases, this number can exceed 15.[1,2]

Whilst the origin of microscopic colitis is largely unknown, it is likely to be multifactorial. Medicines, tobacco and autoimmune conditions have been identified as possible causes.[2] There is evidence that a mucosal immune response occurs in genetically predisposed individuals and may contribute to the development of microscopic colitis.[1] Diarrhoea associated with microscopic colitis is likely caused by mucosal inflammation.[1] Microscopic colitis predominantly affects females and should be considered a possible cause of chronic diarrhoea, especially in middle-aged and older adults.[1,2]

There are two main subtypes of microscopic colitis, and each subtype is based on distinct histopathologic features:[1–3]

- collagenous colitis – a layer of collagen develops in colon tissue
- lymphocytic colitis – the number of lymphocytes (white blood cells) increases in colon tissue.

Collagenous colitis is diagnosed in cases where a broad subepithelial fibrous band is observed on histology.[4] Lymphocytic colitis is diagnosed when an infiltration of more than 20 intraepithelial lymphocytes per 100 epithelial cells is observed.[4]

Diarrhoea, normal colonoscopy results and microscopic abnormalities in the colon are characteristics of both subtypes.[4,5] Biopsies confirm a diagnosis.[1]

Medicines associated with microscopic colitis

The list below provides examples of medicines associated with microscopic colitis (list not exhaustive).

- Non-steroidal anti-inflammatory drugs (NSAIDs): ibuprofen, diclofenac[2, 6-8]
- Proton pump inhibitors: lansoprazole, omeprazole[2, 6-8]
- Histamine-2 receptor antagonists: ranitidine, famotidine[2,9]
- Selective serotonin reuptake inhibitors: sertraline, citalopram[2, 6-8]
- Aspirin[7]
- Clozapine[7]
- Statins: simvastatin, atorvastatin[1]
- Immune checkpoint inhibitors: pembrolizumab[1,10]

Concomitant use of proton pump inhibitors and NSAIDs may also increase the risk of microscopic colitis.[1]

Medicines associated with microscopic colitis are also associated with diarrhoea as a side effect.[4] Healthcare professionals should consider such medicines as a possible cause of microscopic colitis.[1]

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Recent approvals: new active ingredients or new indications

For the period 16 July to 15 October 2022.

Recent approvals of medicines with new active ingredients

Trade name (active ingredient)	Dose form: strength(s)	Therapeutic area
Cresemba (isavuconazonium)	Powder for injection: 200mg Capsule: 100mg	Antifungal agent for treatment of invasive aspergillosis, mucormycosis
Spy Agent Green (indocyanine green)	Powder for injection: 25mg	Fluorescence imaging agent
Entyvio (vedolizumab)	Powder for injection: 300mg	Ulcerative colitis, Crohn's disease
Nubeqa (darolutamide)	Tablet: 300mg	Non-metastatic castration resistant prostate cancer
Evusheld (cilgavimab + tixagevimab)*	Solution for injection: 100mg/mL	Pre-exposure prophylaxis of COVID-19

* Provisional approval

Approved medicines with new indications

There were no approved medicines with new indications for the period 16 July 2022 to 15 October 2022.

See the Medsafe website for:

- more information about these medicines
- data sheets of currently marketed medicines.

Risk of hypoglycaemia with newer antidiabetic medicines

Key messages

- Hypoglycaemia is known to occur with older antidiabetic medicines such as insulin and sulfonylureas.
- Glucagon-like peptide 1 (GLP-1) receptor agonists, sodium-glucose co-transporter 2 (SGLT-2) inhibitors or dipeptidyl peptidase-4 (DPP-4) inhibitors are not typically associated with hypoglycaemia when used as monotherapy, although cases have been reported.
- The risk of hypoglycaemia increases when GLP-1 receptor agonists, SGLT-2 inhibitors or DPP-4 inhibitors are used concomitantly with insulin and/or sulfonylureas. Patients on concomitant therapy may require a lower dose of insulin or the sulfonylurea to prevent episodes of hypoglycaemia.

The Centre for Adverse Reactions Monitoring (CARM) has received 2 case reports of hypoglycaemia associated with newer antidiabetic medicines (one report with vildagliptin and one with empagliflozin). Healthcare professionals should monitor for and discuss the risks of hypoglycaemia when prescribing medicines to treat type 2 diabetes mellitus (T2DM).

Pharmacological treatment of type 2 diabetes mellitus

Pharmacological treatment with glucose-lowering medicines aims to lower HbA_{1c} levels and reduce the risk of diabetes complications.[1]

Many medicines are available to treat T2DM, and the choice of medicine depends on the patient's overall health status, co-morbidities, and risks associated with hypoglycaemia.[1] Metformin, insulin and sulfonylureas (eg, gliclazide, glipizide) are well-known antidiabetic medicines. Newer antidiabetic medicines approved and available in New Zealand include:

- glucagon-like peptide 1 (GLP-1) receptor agonists: dulaglutide, exenatide
- sodium-glucose co-transporter 2 (SGLT-2) inhibitors: dapagliflozin, empagliflozin
- dipeptidyl peptidase-4 (DPP-4) inhibitors: saxagliptin, vildagliptin.

Hypoglycaemia

Hypoglycaemia in patients with diabetes is defined as all episodes of an abnormally low plasma glucose concentration (with or without symptoms) that expose the individual to harm.[2] There is no specific glucose level that defines hypoglycaemia and the glycaemic thresholds that induce symptoms vary between individuals.[3] Hypoglycaemia is associated with an increased risk of falls and cognitive impairment and may increase the risk of mortality.[1]

Hypoglycaemia is known to occur with insulin and sulfonylureas.[4] GLP-1 receptor agonists, SGLT-2 inhibitors and DPP-4 inhibitors are not typically associated with hypoglycaemia when used as monotherapy,[3] although cases have been reported. The risk of hypoglycaemia increases with concomitant use of insulin and/or a sulfonylurea.[3]

Mechanism of action

GLP-1 receptor agonists and DPP-4 inhibitors increase the levels of incretin hormones (glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide).[5,6] Increased levels of these hormones enhance beta cell glucose sensitivity, resulting in improved glucose-dependent insulin secretion and reduced blood glucose.[5,6] Due to this enhanced beta cell sensitivity, patients taking concomitant insulin or a sulfonylurea may require a lower dose of their insulin or sulfonylurea to prevent episodes of hypoglycaemia.[6]

Hypoglycaemia was a very common adverse reaction (frequency ≥1/10) reported in clinical trials of patients taking SGLT-2 inhibitors with concomitant insulin or sulfonylureas.[7] SGLT-2 inhibitors promote glucose excretion by reducing renal absorption of glucose into the blood stream. Patients on concomitant therapy may require a lower dose of their insulin or sulfonylurea to prevent episodes of hypoglycaemia.[7]

CARM reports

As of 30 September 2022, CARM had received the following reports of hypoglycaemia associated with newer antidiabetic medicines.

- Vildagliptin (CARM ID: 138371) – a patient on insulin experienced hypoglycaemia after starting treatment with vildagliptin. The insulin dose was decreased, and they were reported to have recovered.

- Empagliflozin (CARM ID: 142383) – the patient experienced hypoglycaemia after their empagliflozin dose was increased.

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Warfarin: eat, drink and be wary

Key messages

- Warfarin interacts with many medicines, herbal products, dietary supplements and foods.
- Advise patients on warfarin to avoid herbal products and dietary supplements. Patients should also discuss any major dietary changes with their healthcare professional.
- More frequent international normalised ratio (INR) monitoring may be required for patients who take herbal products, dietary supplements or certain foods.

The Centre for Adverse Reactions Monitoring (CARM) recently received a case report (CARM ID: 143662) of a patient taking warfarin who experienced spikes in their INR readings. There is a risk of severe bleeding in patients with high INR.[1] The patient was taking a turmeric tonic in addition to having a diet high in turmeric.

Medsafe previously published a safety communication warning that turmeric/curcumin-containing products can interact with warfarin.[2] CARM continues to receive reports of warfarin interactions.

Advice for prescribers and their patients

The Coumadin and Marevan data sheets include information for prescribers on interactions between warfarin and other medicines, herbal products, dietary supplements and food. The interaction checker on the New Zealand Formulary website can also be used to check for known and theoretical interactions.

Patients may not be aware of warfarin's many interactions, particularly with herbal products, dietary supplements and food. The Coumadin and Marevan consumer medicine information (CMI) leaflets have information for patients about these potential interactions. Health Navigator also has information for patients about warfarin and diet.

Avoid herbal products and dietary supplements[3,4]

Patients taking warfarin must not use herbal products containing St John's Wort (*Hypericum perforatum*). St John's Wort can reduce the clinical effects of warfarin.

Many other herbal products and dietary supplements have a theoretical effect on warfarin, although most of these interactions are not proven. Advise patients that they should generally avoid taking these products while taking warfarin, and to inform their doctor and/or pharmacist if they are taking any. More frequent INR monitoring is advisable if patients are taking herbal products or dietary supplements.

Avoid major changes to diet[3,4]

In addition to herbal products and dietary supplements, certain foods such as liver, broccoli, Brussels sprouts and green leafy vegetables can interact with warfarin. These foods are all high in vitamin K, which has anticoagulant properties. A sudden change in diet can affect anticoagulant control. Inform patients to seek medical advice before making major changes to their diet.

Cranberry and grapefruit juice[3,4]

Patients should avoid cranberry products due to a possible interaction with warfarin. Consider more frequent INR monitoring for any patient taking warfarin and regular cranberry juice. Grapefruit juice may also cause a modest rise in INR in some patients.

New Zealand case reports

As of 30 September 2022, CARM had received a total of 236 reports for warfarin interactions. Of these, 33 were for interactions with food, herbal products and dietary supplements, including 3 with turmeric/*Curcuma longa*.

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Gathering knowledge from adverse reaction reports: December 2022

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: 143883 **Age**: 59 **Gender**: Female **Medicine(s)**: Escitalopram **Reaction(s)**: Galactorrhoea	A few days after starting escitalopram, the patient noted redness and swelling in the nipple and leakage of milk.
	The **Escitalopram** (Ethics) data sheet states that galactorrhoea has been reported as a class effect for SSRIs (selective serotonin reuptake inhibitors).
CARM ID: 143918 **Age**: 55 **Gender**: Female **Medicine(s)**: Budesonide + formoterol **Reaction(s)**: Paradoxical bronchospasm	The patient experienced an increase in wheezing following use of her turbuhaler.
	There is a warning for paradoxical bronchospasm in the **Symbicort Turbuhaler** data sheet.
CARM ID: 144022 **Age:** 82 **Gender:** Female **Medicine(s):** Verapamil, metoprolol **Reaction(s):** Bradycardia, cardiac arrest, drug interaction, shock, ventricular fibrillation	The patient experienced a cardiac arrest due to excessive atrioventricular (AV) blockade. Her verapamil dose had been increased several days earlier and she was taking a number of other medicines, including metoprolol.
	The **Isoptin SR** (verapamil) data sheet states that concomitant therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction, and/or cardiac contractility. There have been reports of excessive bradycardia and AV block, including complete heart block, when the combination has been used for the treatment of hypertension. The combination should be used only with caution and close monitoring. The **Betaloc CR** (metoprolol) data sheet also has information about the interaction.

Case details[a,b]	Reaction description and data sheet information[b,c]
CARM ID: 144385 **Age**: 60 **Gender**: Female **Medicine(s)**: Celecoxib, ibuprofen + paracetamol **Reaction(s)**: Abdominal pain, dizziness, drug interaction, medication error, melaena	The patient experienced abdominal pain, melaena and dizziness. She had been prescribed celecoxib but was also self-medicating with ibuprofen and paracetamol (Maxigesic). The **Celebrex** data sheet has warnings for gastrointestinal effects. It states that celecoxib should not be used with other non-steroidal anti-inflammatory drugs (NSAIDs). The **Maxigesic** data sheet has similar warnings, and states that it should not be taken with any other anti-inflammatory medicines unless under a doctor's instruction. This case serves as a reminder for prescribers to check with patients about over-the-counter medicine use.
CARM ID: 144464 **Age**: 80 **Gender**: Male **Medicine(s)**: Warfarin, miconazole **Reaction(s)**: Drug interaction, INR increased	A patient taking warfarin was prescribed topical miconazole. The patient's international normalised ratio (INR) increased due to a drug-drug interaction between warfarin and miconazole. The **Coumadin** and **Marevan** data sheets state that azole antifungals can potentiate the effect of warfarin. As topical miconazole products are pharmacy-only medicines, they are not required to have a data sheet. However, manufacturer's original packs are required to have the following warning statement: • Patients taking warfarin – talk to a healthcare professional before using [this product/insert name of product].

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.

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 Medicine 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).

Pheochromocytoma crisis and systemic corticosteroids

Key messages

- Pheochromocytoma crisis has been reported following the administration of systemic corticosteroids to patients with pheochromocytoma.
- Pheochromocytomas are tumours in the adrenal medulla that typically secrete one or more catecholamines: epinephrine, norepinephrine and dopamine.
- Pheochromocytoma crisis is a rare, life-threatening emergency in which pheochromocytomas release high levels of catecholamines.

Medsafe has asked sponsors of systemic corticosteroid medicines to update their data sheets with a warning for pheochromocytoma crisis. This article provides information about pheochromocytomas and pheochromocytoma crisis.

Pheochromocytoma

Pheochromocytomas are tumours that arise from chromaffin cells of the adrenal medulla.[1] They typically secrete one or more catecholamines: epinephrine, norepinephrine and dopamine.[2] Pheochromocytomas are rare, with an estimated annual incidence of approximately 0.8 per 100,000 person-years.[1]

Pheochromocytoma predominantly presents with paroxysmal or sustained hypertension, plus episodic headache, tachycardia and sweating due to excessive catecholamine release.[1,3] Diagnosis requires proof of excessive catecholamine release and anatomical documentation of the tumour.[4] The standard treatment for pheochromocytoma is generally pre-operative preparation with an alpha- and beta-blocker and surgical resection.[3,4]

Pheochromocytoma crisis

Pheochromocytoma crisis (PC) is a rare, life-threatening endocrine emergency in which a pheochromocytoma releases high levels of catecholamines.[5] PC can be associated with high mortality rates.[6]

The clinical presentation of PC ranges from severe hypertension to circulatory failure and shock, with subsequent involvement of multiple organ systems, including the cardiovascular, pulmonary, neurological, gastrointestinal, renal, hepatic and metabolic systems.[6] PC can therefore be difficult to diagnose if the patient is not already known to have a pheochromocytoma, as it may mimic other life-threatening conditions.[5]

Management includes initial medical stabilisation of the acute crisis followed by sufficient alpha blockade before surgery.[6]

PC can occur spontaneously or be triggered by tumour resection, trauma, certain medicines (eg, corticosteroids, beta-blockers, metoclopramide, anaesthetic agents) or stress from nonadrenal surgery.[2,6]

Corticosteroid-induced pheochromocytoma crisis[5]

Although several hypotheses exist, the mechanism by which systemic corticosteroids trigger PC is not confirmed. Corticosteroids may potentiate the action of catecholamines on peripheral vessels and the heart, potentially leading to vasculopathy, tissue necrosis and haemorrhage. Increased corticosteroid receptor expression may mediate pheochromocytoma tumour sensitivity to corticosteroids and trigger catecholamine synthesis, production and release.

Consider PC as a differential diagnosis in patients treated with systemic dexamethasone or other corticosteroid products and who present with severe haemodynamic instability, shock, arrhythmia, cardiac ischaemia, or other symptoms suggestive of adrenergic crisis.

Data sheet update

PC is a rare but life-threatening condition. Therefore, Medsafe has requested that sponsors of systemic corticosteroids include the following warning in their data sheets:

> **Pheochromocytoma crisis.** Pheochromocytoma crisis, which can be fatal, has been reported after administration of systemic corticosteroids. Corticosteroids should only be administered to patients with suspected or identified pheochromocytoma after an appropriate risk/benefit evaluation.

As of 30 September 2022, there have been no New Zealand reports of PC following administration of systemic corticosteroids.

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Quiz answers

1. NSAIDs are contraindicated in the third trimester of pregnancy. (September 2022)
2. Trimethoprim or co-trimoxazole can interact with methotrexate to cause bone marrow suppression. (March 2022)
3. Factors that increase the risk of DKA in patients taking SGLT-2 inhibitors include a low carbohydrate diet, dehydration, acute illness, surgery, insulin deficiency from any cause, reduced caloric intake or increased insulin requirements. (December 2022)
4. Systemic ciprofloxacin may decrease the serum concentration of levothyroxine. If patients taking levothyroxine require concomitant ciprofloxacin, instruct them to separate administration by 6 hours; inform them about this potential interaction and the symptoms of hypothyroidism (eg, fatigue, feeling cold, weight gain, constipation); monitor them for any changes in thyroid function. (June 2022)
5. **a.** Paxlovid is a CYP3A inhibitor. Concomitant use with medicines metabolised by CYP3A may lead to clinically serious adverse reactions. (December 2022)
6. Prostaglandin-associated periorbitopathy describes clinical and cosmetic changes in the eye associated with prostaglandin analogues. (September 2022)
7. The risk of venous thromboembolism (VTE) is highest during the first year after starting a combined oral contraceptive (COC) and when restarting after a break of 4 weeks or more. However, VTE may occur at any time during use of a COC. (March 2022)
8. Pethidine, dextromethorphan and tramadol are high-risk opioids for inducing serotonin syndrome when used with serotonergic antidepressants. (September 2022)
9. **b** and **c**. Vitamin E may inhibit platelet aggregation. Tocopheryl quinone (the main oxidation product of alpha-tocopherol) has anticoagulant properties and can interfere with vitamin K metabolism, theoretically causing bleeding. (June 2022)
10. **True**. St John's Wort can reduce the clinical effects of warfarin. Patients taking warfarin must not use herbal products containing St John's Wort. (December 2022)

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