Prescriber Update

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MINISTRY OF HEALTH
MANATŪ HAUORA

Reminder: Counsel patients about symptoms and signs of venous thromboembolism when prescribing combined oral contraceptives

Key messages

- Prescribers are reminded to counsel patients about the symptoms and signs of venous thromboembolism (VTE) when prescribing combined oral contraceptives (COCs).
- Ensure COC users know to seek medical attention if they experience symptoms or signs of VTE.
- Reassess the risk of VTE periodically during COC use as risk factors may change over time.
- Consider the possibility of VTE in COC users who present with non-specific symptoms.

Following the report of a fatal pulmonary embolism (PE) in a young woman on a combined oral contraceptive (COC) in 2021, the Medicines Adverse Reactions Committee (MARC) asked Medsafe to remind prescribers to ensure patients taking COCs are aware of the symptoms and signs of venous thromboembolism (VTE).

Raise awareness of VTE when prescribing COCs

VTE may occur at any time during use of a COC. However, the risk of VTE is highest during the first year after starting a COC and when restarting after a break of four weeks or more.[1,2]

Prescribers are reminded to counsel patients about the symptoms and signs of VTE when starting a COC and to repeat this information from time-to-time during ongoing COC use, as patients may not recall all the information they received initially.

Ensure that patients know to seek medical attention if they have a hot, swollen or painful leg, and/or if they experience chest pain, cough or shortness of breath.

Review the benefit-risk balance for COC use periodically

The risk of VTE associated with COC use is discussed in a previous issue of Prescriber Update.[2] Briefly, evidence from observational studies suggests that current COC use is associated with a 3- to 3.5-fold increase in the risk of VTE compared with non-use.[1]

Despite this increase in the relative risk of VTE compared to non-use, the absolute risk of VTE in current COC users remains low.[1,3] The absolute risk of VTE associated with COC use varies depending on the type of progestogen (Table 1).[3]

Factors that increase the risk of VTE associated with COC use include (but are not limited to) current or previous VTE, inherited or acquired thrombophilia (eg, antiphospholipid syndrome), major surgery, trauma, prolonged immobility, post-partum, smoking, obesity, and older age.[4–6] Prescribers are reminded to periodically reassess the risk of VTE in patients using a COC to ensure the benefits of use continue to outweigh the risks of harm. Consult the New Zealand data sheet for Contraindications (section 4.3) and Special warnings and precautions (section 4.4) relating to specific COCs.

Table 1. Estimated risk of venous thromboembolism (VTE) associated with different types of progestogens contained in combined oral contraceptives (COCs)[a]

Progestogen type	Estimated risk of developing VTE in a year (incidence per 10,000 women)
Levonorgestrel Norethisterone	5–7
Desogestrel Drospirenone Cyproterone[b]	9–12

Notes:

a. Includes progestogens used in COCs containing <50 mcg ethinylestradiol that are currently available in New Zealand.

b. Cyproterone-containing COCs are indicated only for use in women requiring treatment for androgen dependent conditions such as acne (where local treatment or oral antibiotics have not been successful, hirsuitism or androgenic alopecia). See the Ginet and Diane 35 ED data sheets for more information (available at: medsafe.govt.nz/Medicines/infoSearch.asp).

Source: European Medicines Agency. 2014. *Benefits of combined hormonal contraceptives (CHCs) continue to outweigh risks* 16 January 2014. URL: ema.europa.eu/en/documents/referral/benefits-combined-hormonal-contraceptives-chcs-continue-outweigh-risks_en.pdf (accessed 18 January 2022).

Maintain a high index of suspicion of VTE in COC users

Patients with VTE may be asymptomatic or present with non-specific symptoms such as calf tightness, chest pain or cough. Always be mindful of the possibility of VTE in COC users and follow local guidelines for the investigation and management of suspected VTE as necessary.

More information

The Health Navigator website has information for patients and clinicians.

- Deep vein thrombosis
- Pulmonary embolism
- Combined oral contraceptive pill

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Triptan-associated Takotsubo cardiomyopathy: A heartbreak from a headache

Key messages

- Takotsubo cardiomyopathy is a reversible form of cardiomyopathy characterised by transient systolic dysfunction and apical ballooning of the left ventricle.
- Emotional and physical stress are the most well-known triggers of Takotsubo cardiomyopathy. However, this condition has also been reported in association with triptan use.
- If triptan-associated Takotsubo cardiomyopathy is suspected, initiate supportive therapy in hospital.

The Centre for Adverse Reactions Monitoring (CARM) recently received a report of Takotsubo cardiomyopathy associated with rizatriptan use.

Takotsubo cardiomyopathy (TCM)

TCM is an acute reversible form of left ventricular (LV) systolic dysfunction not related to obstructive coronary disease. TCM is also known as stress cardiomyopathy, broken heart syndrome, stress-induced cardiomyopathy, and apical ballooning syndrome. TCM starts abruptly and unpredictably. Signs and symptoms of TCM are similar to an acute myocardial infarction.[1]

TCM is a rare condition first identified in 1990 in Japan and is typically more common in women and older adults.[2] Emotionally or physically stressful events can trigger TCM. Cases have also been reported with substance withdrawal and the use of some medicines.[2]

Internationally, there are a few case reports associating triptan use and TCM. Most of these reports are in patients taking sumatriptan.[1]

Mechanism

The precise mechanism of TCM is not yet fully understood. Catecholamine-induced cardiotoxicity and microvascular dysfunction have been proposed to be involved.[2]

Acute migraines can cause a sudden surge in catecholamine levels and the triptan medicines used to treat migraines cause vasoconstriction. The combination of these effects may rarely induce TCM.[1]

Clinical presentation, diagnosis, and management

The clinical presentation of patients with TCM are similar to those with acute coronary syndrome. The most common presenting symptom is acute substernal chest pain, but some patients present with dyspnoea or syncope. An electrocardiogram, cardiac troponin levels, coronary angiography, and assessment of LV systolic function are generally required to diagnose TCM.[2]

Patients with TCM have a good prognosis. Typically, patients that survive the acute episode of TCM recover systolic LV function within one to four weeks.[3]

Conservative treatment and resolution of the physical or emotional stress usually result in rapid resolution of symptoms. However, some patients can develop acute complications, such as shock and acute heart failure, requiring intensive therapy.[4]

Given the lack of clinical trial data, there is no clear optimal medication regimen or treatment duration for TCM patients. Once haemodynamically stable, patients are treated with standard medicines for heart failure until systolic function is recovered.[4]

New Zealand case report

CARM has only received one case report of TCM (up to 31 December 2021). Following a dose of rizatriptan, the patient developed a sensation of radiating chest heaviness (CARM ID #142597). New Zealand data sheets for rizatriptan and sumatriptan do not list TCM as an adverse event. However, reports of serious coronary events have been associated with triptan medicines.[5,6]

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MARC's remarks: December 2021 meeting

The Medicines Adverse Reactions Committee (MARC) convened via videoconference on 2 December 2021.

The Committee discussed the risks and benefits of **dihydrocodeine** (DHC), an opioid medicine used for pain management, referred under section 36 of the Medicines Act 1981. The Committee considered that there was insufficient evidence to recommend revoking the consent of DHC in New Zealand. However, regulatory actions to improve the safe use of DHC were recommended, including data sheet updates and for the sponsor to supply a Consumer Medicine Information leaflet. The Committee also recommended highlighting to the clinical leaders at the Ministry of Health the inequities in access to pain services and the need for leadership in the correct use of opioids.

The benefits and risks of **Buccaline**, indicated for the oral antibacterial prophylaxis of complications of colds, were discussed. The Committee considered the potential harms associated with Buccaline, which included using as an alternative to well-studied vaccines or medicines. Overall, the Committee agreed there was a lack of efficacy and safety data and recommended that Medsafe request the sponsor to supply a review of the safety and efficacy of their product under section 36 of the Medicines Act 1981.

The Committee reviewed the risk of bleeding associated with **tocopherol** (vitamin E). The Committee considered that there is possibly an association, but there was insufficient evidence to support it, and the clinical significance is not known. The Committee recommended that Medsafe contact the sponsors of oral anticoagulants (ie, medicines that are known to cause bleeding) to review a possible interaction between vitamin E and their products.

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

Interaction reminder: Bone marrow suppression with methotrexate and trimethoprim or co-trimoxazole

Key messages

- Severe bone marrow suppression has been reported in patients on methotrexate who have received trimethoprim or co-trimoxazole (trimethoprim with sulfamethoxazole). Some cases have been fatal.
- Trimethoprim and co-trimoxazole should be avoided in patients taking methotrexate.
- If this drug combination cannot be avoided, warn patients about the symptoms of bone marrow suppression. Advise them to seek immediate medical attention should these symptoms occur.

The Centre for Adverse Reactions Monitoring (CARM) recently received a fatal report of methotrexate toxicity in a patient who had also received trimethoprim.

Trimethoprim and co-trimoxazole have additive bone marrow suppression effects with methotrexate

Trimethoprim or co-trimoxazole (trimethoprim with sulfamethoxazole), when used with methotrexate, increase the risk of bone marrow suppression (also known as myelosuppression).[1] The evidence for this interaction consists of case reports of severe bone marrow suppression in patients on methotrexate who have received trimethoprim or co-trimoxazole. Some cases have been fatal.[2]

Although the mechanism for this interaction is not fully understood, trimethoprim can have additive antifolate effects and when used with methotrexate, lead to increased myelosuppression.[3] Additionally, sulfamethoxazole (in co-trimoxazole) may displace methotrexate from protein binding sites and compete with the renal transport of methotrexate, leading to increased free methotrexate levels.[4]

It is unclear whether increases in free methotrexate levels also occurs with prophylactic doses of co-trimoxazole. Some studies suggest that prophylactic doses might not delay methotrexate clearance. Monitoring of full blood count is recommended.[2,5,6]

Avoid trimethoprim and co-trimoxazole in patients taking methotrexate

In patients taking methotrexate, avoid trimethoprim and co-trimoxazole.[1] In circumstances where the combination cannot be avoided, healthcare professionals should consider the following.

- Seek specialist advice for safely prescribing trimethoprim or co-trimoxazole antimicrobial therapy for patients on methotrexate in primary care.
- Educate patients to seek immediate medical attention if they notice symptoms of bone marrow suppression. These symptoms may include:
  - mouth ulcers, sore throat, fever or chills[1,7]
  - new or non-resolving infections[3]
  - bruising or bleeding more easily than usual[7]
  - anaemia symptoms such as shortness of breath, dizziness and pallor.[7]

- Monitor full blood count. If any abnormalities arise, consider this interaction as a possible cause[8] and seek urgent specialist advice. More frequent monitoring of other laboratory tests such as renal function may be required[3] – refer to local clinical guidelines and the advice from relevant specialists.
- Ensure regular folate supplement is continued or started.[4]

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Out of the blue: Dapsone-induced methaemoglobinaemia

Key messages

- Methaemoglobinaemia is a recognised adverse effect of dapsone and has been reported with oral and topical dapsone use.
- Consider the possibility of methaemoglobinaemia in patients taking dapsone who present with symptoms or signs of hypoxaemia.
- When prescribing dapsone, inform the patient about the risk of methaemoglobinaemia and advise them to seek medical attention if they experience symptoms or signs of methaemoglobinaemia.

Methaemoglobinaemia is a known adverse effect of dapsone

Dapsone is a sulfone antibiotic that inhibits folic acid synthesis to prevent microbial replication. Oral dapsone is indicated for the treatment of leprosy, dermatitis herpetiformis and actinomycotic mycetoma.[1] Topical dapsone is indicated for the treatment of acne vulgaris.[2]

Methaemoglobinaemia is a known adverse effect of dapsone.[2,3] Varying degrees of dose-related methaemoglobinaemia occur in most individuals at daily oral doses of 200 mg or more but may occur at lower doses.[3] Methaemoglobinaemia has also been reported with the use of topical dapsone.[2]

Methaemoglobin is formed when the iron present in haemoglobin has been altered by oxidation from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state.[4] Ferric iron is unable

to bind to oxygen. Furthermore, the presence of ferric iron in the haemoglobin molecule increases the affinity of ferrous iron for oxygen, resulting in a left shift in the oxygen dissociation curve. There is usually a small amount of methaemoglobin in the blood – approximately 1 percent of total haemoglobin. An increase in the proportion of methaemoglobin leads to reduced oxygen delivery to the tissues. At high concentrations, methaemoglobin causes hypoxia and cyanosis.[4,5] Some medicines, including dapsone, have oxidative properties that can increase the proportion of methaemoglobin.[4]

Symptoms and signs of methaemoglobinaemia

The symptoms and signs of methaemoglobinaemia typically correlate with the level of methaemoglobin in the blood. Early symptoms and signs may include cyanosis and skin discolouration, dyspnoea, headache, light-headedness, fatigue, tachycardia, irritability, and lethargy. Severe methaemoglobinaemia may cause respiratory depression, change in mental status, seizures, loss of consciousness and death.[4]

Management of dapsone-induced methaemoglobinaemia

Consider the possibility of methaemoglobinaemia in patients taking dapsone who present with symptoms or signs of hypoxia. Methaemoglobinaemia is confirmed with a blood test. Consult the local laboratory for testing requirements and reference values.

Note that standard pulse-oximetry may be misleading in patients with methaemoglobinaemia.[4] Assessment of oxygen saturation usually requires arterial blood gas analysis.

If methaemoglobinaemia occurs, discontinue treatment with dapsone.[2,3] Management of methaemoglobinaemia may also include use of oxygen and administration of methylene blue.[6] Severe cases may require blood transfusion.

When prescribing dapsone, inform the patient or caregiver about the risk of methaemoglobinaemia and the symptoms and signs to look out for. Advise patients taking dapsone to seek medical attention urgently if they experience symptoms or signs of methaemoglobinaemia.

New Zealand case reports

Up until 31 December 2021, the Centre for Adverse Reactions Monitoring (CARM) had received 15 reports of methaemoglobinaemia, of which 5 were associated with dapsone.

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Recent approvals: New active ingredients or new indications

For the period 16 October 2021 to 15 January 2022.

Recent approvals of medicines with new active ingredients

Trade name (active ingredient)	Dose form and strength(s)	Therapeutic area
Cuprior (trientine)	Film coated tablet 150 mg	Wilson's disease patients who are intolerant to D-penicillamine therapy
Mylotarg (gemtuzumab ozogamicin)	Powder for injection 5 mg	CD33-positive acute myeloid leukaemia
Trikafta (elexacaftor/ tezacaftor/ivacaftor + ivacaftor)	Film coated tablet 100/50/75 mg + 150 mg 50/25/37.5 mg + 75 mg	Cystic fibrosis patients with at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene
Ronapreve (casirivimab/ imdevimab)	Solution for injection or infusion, single-use or multiuse vials 120/120 mg/mL	COVID-19

Approved medicines with new indications

Trade Name (active ingredient)	Dose form and strength(s)	New therapeutic area(s)
Rinvoq (upadacitinib)	Modified release tablet 15 mg	Psoriatic arthritis Ankylosing spondylitis

See the Medsafe website for:

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

Gathering knowledge from adverse reaction reports: March 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: 141772 **Age:** 79 **Gender:** Female **Medicine(s):** Pregabalin **Reaction(s):** Visual hallucination	The patient experienced visual hallucinations following the third dose of pregabalin.
	Hallucination is listed as an uncommon ADR in the Pregablin Pfizer data sheet.

Case details[a,b]	Reaction description and data sheet information[b,c]
CARM ID: 141573 **Age:** 87 **Gender:** Male **Medicine(s):** Amiodarone **Reaction(s):** Skin discolouration	A patient on long-term therapy with amiodarone developed a blue-grey skin discolouration over his cheeks, nose and forehead.
	The Aratac data sheet states some patients have developed skin pigmentation (slate grey/purple colour) of the [sun] exposed areas. This pigmentation can be avoided if doses are kept as low as possible and may also be dependent on treatment duration. If the pigmentation is cosmetically unsightly, amiodarone should be discontinued if alternative therapy is possible.
CARM ID: 141395 **Age:** 1 month **Gender:** Male **Medicine(s):** Fluoxetine **Reaction(s):** Serotonin syndrome	The infant was exposed to fluoxetine via the mother's breastmilk and experienced serotonin syndrome (hypertonia, hyperreflexia, akathisia, weight loss, reflux, distress). The infant was reported to have recovered.
	The Fluox data sheet states that fluoxetine is excreted in human milk and caution should be used when administered to breastfeeding women. Serotonin syndrome is listed as a very rare adverse reaction in the Fluox data sheet.
CARM ID: 141003 **Age:** 29 **Gender:** Female **Medicine(s):** Carbamazepine **Reaction(s):** Purpura	Soon after starting treatment with carbamazepine, the patient experienced non-traumatic bruising on her forearms. Carbamazepine was discontinued and the bruising resolved.
	Purpura (bruising) is listed as a very rare ADR in the Tegretol data sheet. Purpura may be also cutaneous manifestation of thrombocytopenia or agranulocytosis, which are listed in the data sheet as common and very rare ADRs, respectively. Complete pre-treatment blood counts, including platelets, should be obtained at baseline and periodically thereafter.

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 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).

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
	COVID-19	Adverse events following immunisation with COVID-19 vaccines
20/02/22	Monitoring	Buccaline tablets: review of the benefits and risks under section 36 of the Medicines Act 1981
19/02/22	Monitoring	Update – Pregabalin and the possible risk of bullous dermatitis and exfoliating skin reactions
16/02/22	Consultation	Proposed warning and advisory statement relating to the harm of opioid abuse, misuse, and dependence (closes 4 April 2022)
15/02/22	Monitoring	Update – Dihydrocodeine: review of risks and benefits
31/01/22	Dear Healthcare Professional Letter	Ronapreve (casirivimab and imdevimab): reduced neutralisation activity of the antibody combination against the full-length S protein of the Omicron variant of COVID-19 (PDF, 217 KB, 3 pages)
24/12/21	Dear Healthcare Professional Letter	Important information about Ronapreve (casirivimab and imdevimab) supplied in New Zealand (PDF, 362 KB, 3 pages)
22/12/21	Dear Healthcare Professional Letter	Supply of new formulation of Comirnaty (COVID-19 Vaccine) in New Zealand (PDF, 365 KB, 10 pages)
22/12/21	Alert	Medsafe is issuing a warning not to use Goree Beauty Cream with Lycopene, Goree Day and Night Beauty Cream Oil Free, and Golden Pearl Beauty Cream - statement under section 98 of the Medicines Act 1981
20/12/21	Alert	Reminder: Comirnaty vaccination (Pfizer COVID-19 vaccine) can cause myocarditis and pericarditis
06/12/21	Dear Healthcare Professional Letter	Labelling exemption - Cuprior (trientine) 150 mg film-coated tablet (PDF, 265 KB, 2 pages)
03/12/21	Dear Healthcare Professional Letter	Alecensa (alectinib) - Warnings and precautions and specific dose modification guidance for management of haemolytic anaemia (PDF, 243 KB, 2 pages)
22/11/21	Dear Healthcare Professional Letter	Distinguishing between Thrombosis and Thrombosis with Thrombocytopenia (TTS) following COVID-19 (AstraZeneca and Janssen) vaccinations (PDF, 291 KB, 3 pages)
18/11/21	Dear Healthcare Professional Letter	Update on tenecteplase supply shortage (PDF, 2 pages, 373 KB)
17/11/21	Dear Healthcare Professional Letter	Supply of COVID-19 Vaccine AstraZeneca in New Zealand (PDF, 3 pages, 215 KB)

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