

Prescriber Update

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Some medicines need to be prescribed by brand

Key messages

- All generic medicines approved in New Zealand have been shown to be bioequivalent to the brand name innovator product.
- Nevertheless, for some medicines, particularly those with a narrow therapeutic window, avoid changing brands whenever possible as there is a risk of destabilising treatment for these patients.
- It is acceptable, and sometimes necessary, to use different brands of a medicine to achieve the treatment dose.

Generic medicines contain the same active ingredient delivered in the same way as the brand name innovator product. Suppliers of generic medicines must provide evidence that their product is bioequivalent to the innovator product before they are approved by Medsafe. Medicines are considered bioequivalent if the bioavailability (determined by the rate and extent of absorption of the active ingredient into the systemic circulation) is comparable within internationally accepted limits^{1,2}. Medsafe assesses bioequivalence to the innovator product during the pre-market approval process. Medsafe does not usually assess bioequivalence between different generic products.

Approved generic medicines may generally be substituted for the innovator product. However, for some medicines, particularly those with a narrow therapeutic window, very small differences in the bioavailability of the active ingredient between the generic and the innovator product may have clinical implications in some patients.

Examples of medicines that require particular care when changing brands include lamotrigine and levothyroxine.

Lamotrigine

Lamotrigine has recently been the subject of a change in funding by PHARMAC³. The currently funded brand of lamotrigine (Logem) has been approved by Medsafe and shown to be bioequivalent to the innovator product (Lamictal).

Medsafe recommends that prescribers follow the UK Medicines and Healthcare products Regulatory Agency's (MHRA) advice that brand switches for lamotrigine must be managed carefully with close patient monitoring, taking into account factors such as seizure frequency and treatment history⁴. The evidence that lamotrigine has a narrow therapeutic window is inconclusive at present. However, there is information to show that patients find changing brands difficult⁵.

Levothyroxine

Levothyroxine has a complex pharmacokinetic profile with a narrow therapeutic window and requires careful dose titration and monitoring⁶.

A change in formulation of the Eltroxin brand of levothyroxine in 2007 resulted in a large number of patients experiencing problems. Although the new formulation was bioequivalent to the original formulation, the problems experienced by patients highlighted the need for careful monitoring and dose titration with any change to this medicine^{7,8}.

Medsafe has approved three brands of levothyroxine: Eltroxin (50 mcg and 100 mcg tablets), Synthroid (25 mcg, 50 mcg and 100 mcg tablets) and Eutroxsig (50 mcg, 75 mcg, 100 mcg and 200 mcg tablets). Although both Synthroid and Eutroxsig are bioequivalent to Eltroxin, switching between brands should be avoided because even slight differences in

bioavailability of levothyroxine may have a clinical effect. If a brand change is necessary (eg, because of intolerance to a particular product), the patient should be carefully monitored, and the dose titrated.

Levothyroxine (Mercury Pharma) tablets are marketed in New Zealand with provisional consent under section 23 of the Medicines Act 1981. Bioequivalence has not been demonstrated for this product.

Levothyroxine (Mercury Pharma) should only be prescribed for patients who are already taking this product and (1) are known to be intolerant to other available levothyroxine-containing products or (2) changing to another levothyroxine-containing product is not clinically appropriate⁹. New patients should not be started on Levothyroxine (Mercury Pharma).

Different brands can be combined when necessary

Using a combination of tablet strengths from different brands of a medicine to achieve a required dose is acceptable, but the patient should remain on the same brand of each strength tablet. Finding the correct dosage and combination should be based on clinical assessment and laboratory monitoring, where applicable.

More information

More information on generic medicines and bioequivalence is available in a previous edition of Prescriber Update (www.medsafe.govt.nz/profs/PUArticles/September2017/TheMedsafeFiles4NMAssessment.htm).

You can search for medicine data sheets on the Medsafe website (www.medsafe.govt.nz/Medicines/infoSearch.asp).

References

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The Medsafe Files – Episode 12: Benefit-risk (of harm) review

Key messages

- Medsafe approves medicines based on a favourable balance of benefit to risk of harm for the intended treatment population. The evidence supporting this decision is outlined in the data sheet.
- For each individual patient, the benefits and risks of harm of a medicine need to be personalised for their specific needs and circumstances to make sure the medicine is right for them.

Introduction

Medsafe reviews the benefit and risk of harm of medicines at different stages of the product lifecycle. For example, the benefit-risk balance is assessed:

- prior to approval
- for new indications or changes to indications
- following identification of a significant new adverse reaction
- following identification of new information suggesting a lack of (relative) efficacy or quality issue.

Medsafe reviews the benefits and risk of harm for medicines at the population level. The benefits and risks of harm may be different for an individual considering treatment with that medicine.

Benefit

The benefit of a medicine is the sum of its efficacy and the context of use. Medsafe considers the following information when assessing the benefits of a medicine.

The epidemiology and natural history of the disease targeted by the medicine

Understanding the target condition helps to put the benefits and risks of harm of a medicine into perspective. Tolerance of harm is generally greater for life-threatening conditions such as cancer than self-limiting conditions such as a cold.

The purpose or intended outcome of treatment

Treatments that can cure a disease tend to be associated with a higher harm tolerance than those that reduce the symptoms of a disease. Similarly, vaccines are generally given to healthy people and therefore must be highly effective and safe to satisfy regulatory requirements.

The evidence for benefits

The efficacy of the medicine is a major consideration. The strength of the evidence is a significant part of the evaluation and Medsafe looks at not just the quality of the clinical trial(s) but also the choice of endpoints (outcomes or surrogate markers), the absolute effect of the intervention and its comparison to the background rate of remission for that condition, placebo effects and other interventions (if that data is available).

Also important are quality of life measures and patient views on acceptability and tolerability.

The generalisability of the clinical trial results may be reflected in the approved indication. Indications for medicines when the trials involved very specific patient groups will often restrict use to these groups.

For reviews taking place after the medicine has been approved and used in non-clinical trial populations, data on effectiveness (ie, the benefit in real world use) and comparison with other treatments will also be considered.

Risk of harm

When assessing the risk of harm both the frequency and severity of the harm are considered.

The strength of the evidence for the adverse reaction

During the pre-market approval phase this will generally be the information generated in the clinical trials. The collection of safety information in trials may be driven by prior knowledge of other medicines in the same class, pharmacokinetics, pharmacodynamics and pre-clinical information.

Once the medicine has been approved, additional information becomes available – for example, from case reports and observational studies – enabling the identification of rarer side effects.

Identification of the reaction(s) which are the risk driver(s)

For most medicines there are one or two reactions that have the greatest impact on the balance of benefits and harms. Examples of reactions considered to be risk drivers include: liver toxicity, renal toxicity, haematological toxicity, malignancy, QT-prolongation, and Serious Cutaneous Adverse Reactions (SCAR). A change in the frequency or seriousness/ severity of these reactions is likely to prompt a risk benefit review.

Nature of the reaction

The ability to predict and therefore prevent an adverse reaction is an important consideration. If it is possible to predict a reaction by monitoring factors such as white cell count, the risk may be considered acceptable. These factors are often described in the contraindications or warnings in the data sheet.

Other reactions may be reversible on stopping the medicine or be treatable, and again this will influence their importance relative to the benefits of the medicine. Other reactions may be viewed as more minor or rare enough not to impact the benefit-risk balance.

Risk comparison

It may be possible and appropriate to compare the risks of harm of a medicine with the risks of other medicines used to treat the same condition, as well as the potential effects of not treating the condition.

Risk quantification

The frequency of a reaction may be estimated in clinical trials. However, this can be harder for rarer events only detected once the medicine is in use. When a frequency estimate can be made this is detailed in the data sheet. A change in the frequency of significant reactions can impact the benefit-risk balance and it is important therefore to study the safety of medicines throughout their life cycle.

Overall conclusions on benefit risk

The benefit-risk balance cannot be expressed as a number because while some of the considerations are quantitative, others are qualitative. The unit of measurement differs

between benefit and risk. In particular, long-term benefits may have to be weighed against short term risks or vice versa. The tolerance for risk will also differ according to the expected benefit of the medicine. Therefore, concluding whether the benefits outweigh the risks of harm for a medicine comes down to a value judgement. Decision making tools can be useful to identify how different value judgements may influence the interpretation of the benefits and risks. Where a medicine has more than one indication, the benefit-risk balance is likely to be different for each indication and depends on its context of use.

Other factors that may be considered by the regulator are the ability to impose risk management strategies such as regular blood monitoring or pregnancy prevention programmes, and the statutory power of the regulator.

What about individual patients?

The acceptability of a medicine for an individual patient will depend upon their personal objectives and lifestyle. Therefore, patients need to be involved in the decision-making process.

When considering harm from the patient perspective, drawbacks such as any requirement for routine monitoring or dietary precautions should also be discussed. The route of administration may be unacceptable, or the patient may have difficulties understanding complex administration instructions.

The applicability of the clinical trial benefits will depend on how closely the patient fits the trial inclusion and exclusion criteria. The patient may be in a known higher risk group for harms or may be taking other medicines or natural health products that may interact to cause harm.

When discussing the evidence for benefit and harm, the data should be communicated in a transparent way. Explaining the change of benefit may be best understood using the number of patients needed to treat. Explaining risk may need to include the risk of harm and the risk of not having the reaction. For example, 1 in 10 people who take this medicine experience a headache; 9 in 10 people who take this medicine do not experience a headache. The decision to take the medicine is essentially a gamble by the patient as to whether they will be in the group who will experience the benefit and/or harm. Different patients will have different views on the acceptability of this gamble.

The benefit-risk balance can change over time and the use of medicines should be reassessed periodically and discussed with the patient. Some medicines are known to have a different benefit-risk balance in patients with particular genetic profiles. For example, patients with HLA-B*57:01 should not take abacavir³.

Further reading

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Photosensitivity reactions – The other side of summer

Key messages

- Photosensitivity reactions are possible with a number of medicines and are commonly reported during summer.
- If it is not possible to avoid the photosensitising medicine, advise patients to follow sun protection strategies to stay safe in the sun.

As the weather gets warmer, consider the risk of photosensitivity reactions. Photosensitivity reactions occur with a number of medicines and result in sunburn or dermatitis on sun-exposed skin^{1,2}.

Drug-induced photosensitivity reactions occur after exposure to a topical or systemic photosensitising medicine and exposure to ultraviolet (UV) or visible radiation¹. The reactions can be classed as either phototoxic or photoallergic³.

Phototoxic reactions

Phototoxic reactions are more frequent than photoallergic reactions. They occur within minutes to hours after exposure to light and result from cellular damage^{1–3}. Signs include an exaggerated sunburn reaction, vesicles, blisters and bullae². The reaction is restricted to sun-exposed skin².

Photoallergic reactions

Photoallergic reactions are immune-mediated and take a longer time (24–72 hours) to appear after exposure to light^{1,2}. Photoallergic reactions are eczematous and itchy and may spread to non-exposed areas of skin².

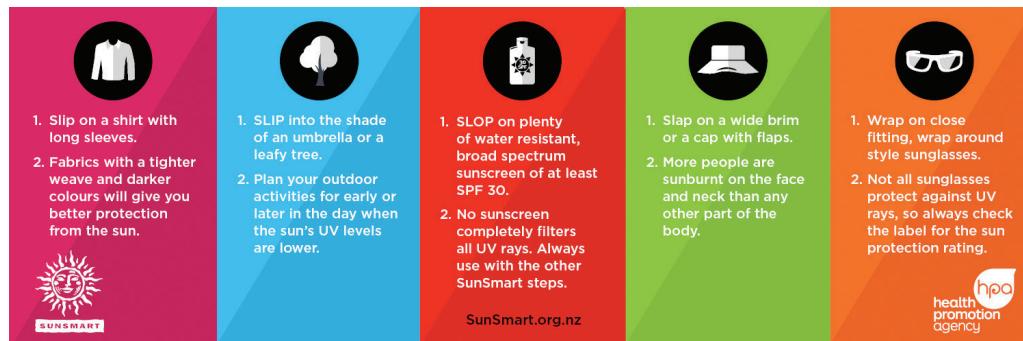
Treatment

The best treatment option is to avoid the photosensitising medicine². If it is not possible to discontinue the medicine, the following sun protection strategies are recommended.

How to be SunSmart⁴

- Slip on a shirt/top with long sleeves and a collar.
- Slip into the shade.
- Slop on sunscreen that is at least SPF 30, broad-spectrum and water resistant. Apply 20 minutes before going outside and reapply every 2 hours.
- Slap on a broad-brimmed hat that shades the face, head, neck and ears.
- Wrap on close fitting sunglasses.
- Don't use sunbeds.

Visit the SunSmart NZ website (www.sunsmart.org.nz) to learn more about staying safe in the sun.



What medicines cause photosensitivity?

A variety of medicines have been associated with photosensitivity reactions including antibiotics, cancer medicines, cardiovascular medicines, some decongestants and antihistamines, medicines to treat diabetes, diuretics, hormones, nonsteroidal anti-inflammatory drugs (NSAIDs), psychiatric medicines and retinoids^{2,5}. See the DermNet NZ website for a list of photosensitising medicines (www.dermnetnz.org/topics/drug-induced-photosensitivity/).

The arrival of summer is a good opportunity to review any new medicines started by your patients for photosensitivity. For example, vemurafenib (brand name Zelboraf) is a relatively new medicine that has been associated with mild to severe photosensitivity⁶. Patients should avoid sun exposure when taking Zelboraf⁶.

Refer to the medicine data sheet for further information on photosensitivity reactions for each specific medicine (www.medsafe.govt.nz/Medicines/infoSearch.asp).

References

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Do not use modafinil in pregnant patients or those who may become pregnant

Key messages

- Modafinil is contraindicated in patients who are pregnant or may become pregnant.
- The effectiveness of oral contraceptives may be reduced when used with modafinil. Alternative or concomitant methods of contraception are recommended during treatment with modafinil and for two months after stopping treatment.

Modafinil is indicated to improve wakefulness in people with excessive daytime sleepiness associated with narcolepsy, obstructive sleep apnoea/hypopnoea syndrome (OSAHS), or shift work sleep disorder (SWSD)¹.

Modafinil is contraindicated during pregnancy

This contraindication was recently updated and extended to include patients who may become pregnant.

The contraindication was updated because modafinil is suspected to cause congenital malformations when administered during pregnancy. This suspicion comes from limited human experience from a pregnancy registry and spontaneous reporting. There are no well-controlled trials with modafinil in pregnant women.

Women of childbearing potential must use effective contraception

Modafinil may reduce the effectiveness of oral contraception due to enzyme induction. Alternative or concomitant methods of contraception are recommended during treatment with modafinil and for two months after stopping treatment. The data sheet is being updated with this information.

Refer to the data sheet for full prescribing information (www.medsafe.govt.nz/profs/Datasheet/m/Modavigiltab.pdf).

Reference

1. Teva Pharma New Zealand Ltd. 2019. *Modavigil New Zealand Consumer Medicine Information* September 2019. URL: www.medsafe.govt.nz/Consumers/CMI/m/modavigil.pdf (accessed 15 October 2019).

Ibuprofen and impaired renal function: Keep your fluids up

Ibuprofen is associated with a risk of impaired renal function. The two major metabolites of ibuprofen are excreted mainly in the urine¹. The risk of impaired renal function is increased in patients who are dehydrated, especially children and adolescents¹.

The Centre for Adverse Reactions Monitoring (CARM) has received five reports of patients who experienced acute kidney injury associated with ibuprofen in which dehydration was considered a possible contributing factor (CARM IDs: 24886, 34497, 88838, 126380, 132513).

Ibuprofen is widely used for the temporary relief of pain and/or inflammation and is available over the counter and with a prescription. When prescribing ibuprofen, consider whether the patient is adequately hydrated. This is especially important over the upcoming summer season and for people participating in sports.

Reference

1. Mylan New Zealand Ltd. 2019. *Brufen New Zealand Data Sheet* June 2019. URL: www.medsafe.govt.nz/profs/Datasheet/b/brufen200mgtab.pdf (accessed 30 September 2019).

We need your help!



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

Medicine	Potential safety issue	Active monitoring ends
Dabigatran	Vasculitis	14/05/2020

- M² (Medicines Monitoring) is a Medsafe scheme designed to collect more information on potential safety signals for specific medicines.
- Please send your report to CARM (as for any suspected adverse reaction). This can be done even if the reaction happened some time ago. Please include as much information as possible as this helps the medical assessors at CARM to investigate whether the medicine caused the reaction.
- For further information about M², see the Medsafe website (www.medsafe.govt.nz/profs/M2MedicinesMonitoring.asp).

* The appearance of a possible safety issue in this scheme does not mean Medsafe and CARM have concluded that this medicine causes the reaction.

Gathering knowledge from adverse reaction reports: December 2019

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

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

Case details ^a	Reaction description and data sheet information ^b
CARM ID: 130562 Age: 15 Gender: Female Medicine(s): Infliximab Reaction(s): Systemic lupus erythematosus (SLE), arthritis	A female patient with Crohn's disease experienced polyarthritis in her fingers and toes one week after her routine infliximab dose. The rheumatologist diagnosed TNF inhibitor-induced SLE. Lupus-like syndrome is listed as an uncommon immune disorder in the Remicade data sheet (www.medsafe.govt.nz/profs/Datasheet/r/Remicadeinj.pdf).
CARM ID: 132796 Age: 64 Gender: Male Medicine(s): Vemurafenib Reaction(s): Stevens-Johnson Syndrome (SJS)	Eight days after commencing vemurafenib, a male patient was reported to have developed SJS with extensive skin, mucosal and conjunctival involvement. SJS is listed in the Zelboraf data sheet (www.medsafe.govt.nz/profs/Datasheet/z/zelborafatab.pdf).
CARM ID: 133495 Age: 44 Gender: Male Medicine(s): Mesalazine Reaction(s): Myocarditis, pericarditis	A patient using both mesalazine suppositories and taking oral mesalazine developed chest pain, ECG changes and raised troponins. Mesalazine-induced myocarditis was suspected. Cardiac hypersensitivity reactions (myocarditis and pericarditis or pleuropericarditis) are described in the warnings and precautions sections of the Pentasa (www.medsafe.govt.nz/profs/Datasheet/p/Pentasatabgranenemasuppos.pdf), Asacol (www.medsafe.govt.nz/profs/Datasheet/a/Asacoltabsupposenema.pdf) and Asamax (www.medsafe.govt.nz/profs/Datasheet/a/Asamax500tab.pdf) data sheets.

Case details ^a	Reaction description and data sheet information ^b
<p>CARM ID: 133238</p> <p>Age: 70</p> <p>Gender: Female</p> <p>Medicine(s): Cannabidiol; Tetrahydrocannabinol</p> <p>Reaction(s): Suicidal ideation, confusional state, paranoia, urinary incontinence</p>	<p>A female patient started taking Sativex, increasing over a month to 5 sprays a day. She experienced confusion, paranoia, suicidal ideation and loss of bladder control. She stopped taking Sativex and was reported to have recovered.</p> <p>Disorientation is listed as a common undesirable effect in the Sativex data sheet, with paranoia and suicidal ideation listed as uncommon effects.</p> <p>The data sheet states that disorientation (or confusion), hallucinations and delusional beliefs or transient psychotic reactions have also been reported and in a few cases a causal association between Sativex administration and suicidal ideation could not be ruled out. In any of these circumstances, Sativex should be stopped immediately and the patient monitored until the symptom has completely resolved (www.medsafe.govt.nz/profs/datasheet/s/sativexspray.pdf).</p>
<p>CARM ID: 133283</p> <p>Age: 68</p> <p>Gender: Female</p> <p>Medicine(s): Tetrabenazine</p> <p>Reaction(s): Facial paralysis, dysarthria, dysphagia</p>	<p>A female patient taking quetiapine and olanzapine was started on tetrabenazine. Two weeks later, she experienced progressive dysphagia and dysarthria, which rapidly worsened and she developed severe pseudobulbar palsy. Tetrabenazine was stopped and the patient made a gradual recovery over the next four weeks.</p> <p>The Motetis data sheet states that tetrabenazine can induce Parkinsonism. There is a potential for significant dopamine depletion when administering tetrabenazine concomitantly with neuroleptic agents, and patients should be monitored clinically for the development of Parkinsonism (www.medsafe.govt.nz/profs/Datasheet/m/motetistab.pdf).</p>
<p>CARM ID: 133320</p> <p>Age: 6</p> <p>Gender: Male</p> <p>Medicine(s): Methylphenidate</p> <p>Reaction(s): Alopecia</p>	<p>Shortly after starting methylphenidate, a male patient developed alopecia. The medication was stopped, and his hair was reported to have almost fully regrown a few months later.</p> <p>Scalp hair loss is listed as a common adverse reaction in the Rubifen (www.medsafe.govt.nz/profs/Datasheet/r/rubifentabsrtab.pdf) and Ritalin (www.medsafe.govt.nz/profs/Datasheet/r/RitalintabSRtabLAtab.pdf) data sheets.</p>

Notes:

- Only the medicines suspected to have caused the reaction are listed in the table.
- If the suspect medicine's brand name is not described in the report to CARM, only the data sheet for the funded medicine is included in the table.

Information about suspected adverse reactions reported to CARM is available on the Medsafe website using the Suspected Medicines Adverse Reaction Search (SMARS) (www.medsafe.govt.nz/Projects/B1/ADRSearch.asp).

By selecting the ingredient of a medicine, you can find out:

- the number of reports and suspected adverse reactions for that ingredient. The suspected reactions are grouped by body system or organs (Summary report)
- single case reports, listing the medicines involved that contain the ingredient and the suspected adverse reactions (Detail report).

The use of serotonin reuptake inhibitors in children and adolescents

Key messages

- Serotonin reuptake inhibitors (SRIs) are not approved for use in children and adolescents for depression or anxiety.
- Suicidality (suicidal thoughts and behaviours) has been associated with the use of SRIs, particularly in children and adolescents.

Introduction

Serotonin reuptake inhibitors (SRIs) are not approved in New Zealand for use in children and adolescents for depression or anxiety¹⁻⁴. For the purposes of this article, SRIs includes selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs).

Section 25 of the Medicines Act 1981 permits an authorised prescriber to use any medicine (approved or unapproved) for the treatment of a particular patient in his or her care⁵. However, regardless of whether the authorised prescriber uses approved or unapproved medicines, he or she must provide care of an adequate professional and ethical standard⁵. The decision to use SRIs in children and adolescents should be made in consultation with the patient and their parents/caregivers, ensuring that they are fully informed about the potential benefits and harms of taking the medicine.

The Best Practice Advocacy Centre New Zealand (bpac^{NZ}) recommends non-pharmacological approaches as the preferred first line treatment for patients aged under 18 years with anxiety disorders or depression⁶. Treatment should acknowledge the ongoing importance of family support, sleep, good nutrition and exercise⁶. Local clinical guidelines should also be considered.

Usage data

Fluoxetine was the most frequently dispensed SRI in children between 2014/15 and 2018/19, as shown in Table 1 (children and adolescents aged under 18 years) and Table 2 (children aged under 12 years).

Table 1: Number of children and adolescents aged under 18 years who have received at least one initial dispensing of SRIs between 2014/15 and 2018/19

Financial Year	Number of children and adolescents aged under 18 years			
	Citalopram	Fluoxetine	Paroxetine	Venlafaxine
2014/15	1913	4965	232	281
2015/16	1951	5475	225	327
2016/17	1715	5815	236	387
2017/18	1538	6223	177	403
2018/19	1441	6680	161	356

Source: The data is sourced from the Pharmaceutical Collections as at 21 July 2019. The data is not a validated statistic and therefore considered unofficial. However, it provides a good estimation of how many children and adolescents are receiving SRIs and the trends over time.

Table 2: Number of children aged under 12 years who have received at least one initial dispensing of SRIs between 2014/15 and 2018/19

Financial Year	Number of children aged under 12 years			
	Citalopram	Fluoxetine	Paroxetine	Venlafaxine
2014/15	166	536	5	1
2015/16	168	588	3	9
2016/17	157	653	7	8
2017/18	133	725	7	5
2018/19	132	740	6	1

Source: The data is sourced from the Pharmaceutical Collections as at 21 July 2019. The data is not a validated statistic and therefore considered unofficial. However, it provides a good estimation of how many children are receiving SRIs and the trends over time.

New Zealand case reports

From 1 July 2014 to 30 June 2019, the Centre for Adverse Reactions Monitoring (CARM) received 27 case reports in patients aged under 18 years, where at least one of the suspect medicines was an SRI. There were:

- 2 reports for citalopram
- 19 reports for fluoxetine
- 3 reports for sertraline
- 4 reports for venlafaxine.

(One case report was for a patient taking fluoxetine and sertraline, so the sum of the medicine reports does not match the number of case reports.)

The adverse effects reported included (in alphabetical order): abdominal discomfort, abnormal behaviour, abnormal feelings, aggression, confusion, drug interaction, dyspnoea, electric shock sensation, fever, flatulence, gastroesophageal reflux, hallucinations, headache, malaise, muscle contractions, nausea, panic, pruritus, rash, somnolence, tiredness, tremor and vertigo. Muscle contractions could indicate possible serotonin syndrome.

Six reports were associated with changing brand of SRI.

There was one report of suicidal tendency (CARM ID number 113375), where fluoxetine and sertraline were both the suspect medicines.

Adverse events in young patients tend to be more common and more severe, so it is important to closely monitor a child or adolescent who has been prescribed an SRI⁶.

Suicidality

Suicidality (suicidal thoughts and behaviours¹) is associated with a number of medicines, including SRIs^{7,8}.

Prescribers are reminded to inform patients and their parents/caregivers of an increased risk of suicidality with SRIs⁷. Advise patients to seek medical advice immediately if they experience changes in mood or behaviour that may be suggestive of suicidality⁷. Clinicians should also be alert to signs of akathisia, as this may be associated with suicidality⁸.

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Recent approvals of medicines containing a new active ingredient

For period 16 July 2019 to 15 October 2019.

Trade Name (Active ingredient)	Dose form and strength(s)	Therapeutic area
Fotivda (tivozanib)	Capsule 890 mcg 1340 mcg	Renal cell carcinoma

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

MARC's Remarks: September 2019 meeting

The Medicines Adverse Reactions Committee (MARC) met on 12 September 2019 to discuss a number of medicine-related safety issues.

Based on case 132801 reported to the Centre for Adverse Reactions Monitoring (CARM), the MARC recommended that a submission is made to the Medicines Classification Committee to review the classification of Bonjela (**choline salicylate**).

The MARC discussed benefits and risks of harm of **Cafergot** (ergotamine tartrate + caffeine) under section 36 of the Medicines Act 1981. Cafergot is indicated for the treatment of acute attacks of migraine with or without aura in adults. The MARC considered the benefits of use of Cafergot no longer outweigh the risks of harm. The MARC therefore recommended that consent to distribute Cafergot in New Zealand be revoked. The MARC recommended a 6-month transition period to enable patients to change to alternative treatment.

The MARC discussed the use of **topiramate** for migraine prevention during pregnancy and recommended that topiramate should not be used to treat migraine in women of child bearing potential unless they are taking adequate contraception.

The MARC discussed **serotonin reuptake inhibitors** and the risk of persistent sexual dysfunction. The MARC recommended data sheet updates to outline this risk for serotonin reuptake inhibitor products.

A benefit-risk review of **dextromethorphan** was also considered. The MARC discussed the available evidence presented to them and considered that, although marginal, the benefit-risk balance was favourable. The MARC recommended that data sheets should contain information on dependence, serotonin syndrome and overdose for dextromethorphan-containing products. The MARC noted they are fully in favour of the reclassification of dextromethorphan to Pharmacist Only.

The MARC reviewed the Risk Management Plan (RMP) for the **recombinant varicella zoster virus vaccine** (Shingrix) and considered the RMP to be thorough, appropriate and complete at this time.

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

Quarterly summary of recent safety communications

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

Date	Communication	Topic
20/11/2019	Alert	Consent to distribute Cafergot tablets (ergotamine tartrate 1 mg + caffeine 100 mg) will be revoked under Section 36 of the Medicines Act 1981 on 1 May 2020
14/11/2019	Monitoring	M ² Possible risk of vasculitis with dabigatran (Pradaxa)
12/11/2019	Monitoring	Suspected adverse reaction reports to lamotrigine after changing brands
12/11/2019	Monitoring	Update – Breast Implants and anaplastic large cell lymphoma
7/11/2019	Monitoring	Everet (levetiracetam) – supply and potential seizure control issues for patients
6/11/2019	Alert	Consumer level recall of one lot of Avonex Pen 30mcg in 0.5mL, Lot 1422362
21/10/2019	Monitoring	Losartan approved medicines supplied in New Zealand not affected by recalls overseas
21/10/2019	Monitoring	Review of chemically synthesised active pharmaceutical ingredients for presence of nitrosamine impurity
21/10/2019	Alert	Medicines containing ranitidine and a potential impurity, N-nitrosodimethylamine (NDMA)
11/10/2019	Alert	Medsafe is issuing a warning that Valentus SlimROAST Optimum Dark Roast Coffee should not be consumed – statement under section 98 of the Medicines Act 1981
11/10/2019	Alert	Surgical Mesh Implants – Adverse Event Reporting and Monitoring – Link to the latest October 2019 report
25/09/2019	Dear Healthcare Professional Letter	MMR II Vaccine – Additional supply of MMR II measles, mumps and rubella vaccine: differences in labelling and package inserts
23/09/2019	Alert	Medicines containing ranitidine and a potential impurity, N-nitrosodimethylamine (NDMA)
19/09/2019	Monitoring	Update – M ² Possible risk of lichen planus or lichenoid drug eruption with zoster (shingles) vaccine or influenza vaccine

Haemolytic anaemia – Sometimes caused by medicines

Key messages

- Medicines can cause haemolytic anaemia via immune reactions or oxidative damage.
- Consider medicines as a possible cause of unexplained haemolytic anaemia. Discuss with a haematologist or transfusion medicine specialist.

What is haemolytic anaemia?

Haemolytic anaemia is characterised by a low number of circulating red blood cells (RBC) due to their premature destruction (haemolysis) and an elevated reticulocyte count¹. There are many causes, including medicines, autoimmune or congenital disorders, infections, transfusions and toxins¹.

Symptoms can include weakness, dizziness, dyspnoea, jaundice, dark urine, mild pallor or splenomegaly². Severe haemolysis can cause hepatosplenomegaly, haemoglobinuria and heart failure². Rarely, immune haemolytic anaemia may be fatal⁴.

How can medicines cause haemolytic anaemia?

Haemolytic anaemia may occur within hours of exposure to a medicine or after several months of exposure³. There are two main mechanisms by which medicines can cause haemolytic anaemia: immune haemolysis and oxidative damage⁵.

Immune haemolysis

Immune haemolysis generally refers to RBC destruction by autoantibodies and/or complement proteins bound to the RBC surface¹. The medicine may alter antigens on the RBC, resulting in the production of autoantibodies that cross-react with the unaltered antigen, or the medicine may associate with structures on the red cell and be part of the antigen in a haptenic reaction⁶.

More than 130 medicines have been associated with immune haemolytic anaemia but the most commonly reported include second- and third-generation cephalosporins, diclofenac, rifampicin, oxaliplatin and fludarabine³.

Transient but clinically significant haemolytic anaemia has been reported following high-dose infusion of intravenous immunoglobulin due to the presence of anti-A, anti-B, and occasionally anti-D or other erythrocyte antibodies in the product⁷. These antibodies coat recipient RBC, producing immune, but not autoimmune haemolysis⁵.

Oxidative damage

Medicines with oxidative potential can cause haemolytic anaemia in all patients, but those with glucose-6-phosphate dehydrogenase (G6PD) deficiency (and other inherited conditions) are at higher risk⁵. G6PD deficiency is an inherited disorder caused by a genetic defect in the RBC enzyme G6PD, which protects RBCs from oxidative injury⁸.

Medicines with oxidative potential that may be unsafe for patients with G6PD include dapson, methylene blue, nitrofurantoin, primaquine, quinolones, rasburicase and sulphonamides^{5,9}.

Clinical and laboratory findings

There is no single specific diagnostic test for haemolytic anaemia¹. Patients with haemolytic anaemia usually have an increased reticulocyte count that is not explained by recent bleeding or recent correction of iron deficiency or other nutrient deficiency¹. Patients may

also have evidence of RBC destruction, including increased lactate dehydrogenase and bilirubin, decreased haptoglobin, and RBC shape changes on the peripheral blood smear¹.

Immune haemolysis is characterised by a positive direct antiglobulin test (DAT; also called direct Coombs test) and/or a positive indirect antiglobulin test (also called indirect Coombs test)¹.

Management

In cases of unexplained haemolytic anaemia, consider medicines as a possible cause. Check the data sheet to determine whether haemolytic anaemia is a known reaction for that medicine (data sheets are available from www.medsafe.govt.nz/Medicines/infoSearch.asp).

Management of haemolytic anaemia is dependent on the cause and severity. Sometimes, discontinuation of the medicine is sufficient. In other cases, interventions, such as transfusion, may be required. Consult a haematologist or transfusion medicine specialist for advice.

New Zealand reports

Since 2010, the Centre for Adverse Reactions Monitoring (CARM) has received 51 reports (with 59 suspected medicines) where the reported reactions included haemolytic anaemia and/or a positive direct Coombs test.

Table 1 shows the medicines most frequently reported to CARM, and the number of positive dechallenges (withdrawal of medicine and cessation of symptoms) and rechallenges (restarting the medicine and recurrence of symptoms).

Table 1: Medicines most frequently reported to CARM for haemolytic anaemia and/or a positive direct Coombs test, 1 January 2010 to 30 September 2019

Medicine	Reports	Positive dechallenge ^a	Positive rechallenge ^b
Immunoglobulin normal	33	17	2
Amoxicillin/clavulanic acid	4	3	
Dapsone	2	1	
Sulphasalazine	2	2	

Notes:

a. Positive dechallenge: withdrawal of the medicine and cessation of symptoms.

b. Positive rechallenge: restart the medicine and recurrence of symptoms.

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A drop in the eye has widespread ripples

Key messages

- Some eye drops can cause systemic adverse reactions.
- Only a small proportion of each dose is retained in the eye.
- Systemic absorption may be reduced by:
 - closing the eye and/or pressing a clean forefinger where the lower eyelid meets the nose
 - waiting at least 5–10 minutes between applying drops to the same eye.

Background

The Centre for Adverse Reactions Monitoring (CARM) recently received the first report of a patient who developed confusion and psychosis approximately one week after starting treatment with prednisolone eye drops (CARM ID: 132498). The symptoms slowly resolved on stopping the prednisolone eye drops.

Where does the eye drop go?

Eye drops can cause systemic adverse reactions. It is estimated that only 5–10 percent of the active medicine included in an eye drop remains in the eye, and up to 80 percent may reach the general circulation. Because of poor bioavailability, the dose of the active ingredient in eye drops often needs to be comparatively high¹.

How much remains in the eye depends on a variety of factors, such as the characteristics of the eye drop and administration technique. Infants, pregnant and nursing women and aged patients are particularly at risk for systemic adverse reactions from eye drops².

Tears and eye drops drain through a small canal into the nose which is lined with nasal mucosa containing many blood vessels. Once in contact with the vascular nasal mucosa, relatively rapid absorption of the active ingredient into the bloodstream can occur avoiding the first passage through the liver^{1,3}.

A second drop instilled immediately after the first results in an even higher proportion of active ingredient passing into the nasal mucosa¹.

What do the data sheets say?

The New Zealand data sheets for prednisolone eye drops 1% solution state that, although systemic effects are extremely uncommon, there have been rare occurrences of systemic hypercorticoidism after use of topical steroids^{4,5}.

Exogenous glucocorticoids such as prednisolone can lead to Cushing's syndrome, which includes psychiatric disturbances.

Can systemic absorption be avoided?

Systemic absorption can be significantly reduced by:^{1,3,6}

- keeping the eyelid gently closed for 2–3 minutes after instilling drops
- applying gentle pressure over the tear duct with a clean finger for 3 minutes after instillation
- waiting at least 5–10 minutes between eye drops, if more than one drop is required.

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Reminder: Avoid using CYP2D6 inhibitors with tamoxifen

Tamoxifen is a prodrug metabolised by CYP2D6 into its active metabolite, endoxifen¹. Endoxifen concentrations are about 75 percent lower in patients who lack CYP2D6 compared to those with normal CYP2D6 activity². Co-administration of strong CYP2D6 inhibitors reduces endoxifen levels to a similar extent².

Avoid using CYP2D6 inhibitors such as paroxetine and fluoxetine with tamoxifen². Prescribe an alternative antidepressant with little or no inhibition of CYP2D6 for patients who require antidepressant treatment while taking tamoxifen³. These may include citalopram, escitalopram, sertraline, mirtazapine and venlafaxine³.

The Centre for Adverse Reactions Monitoring (CARM) has received a report describing an interaction between tamoxifen and fluoxetine (CARM ID 115253). This co-administration resulted in reduced therapeutic response and progression of disease.

References

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Liquorice – All sorts of side effects and interactions

Key messages

- Liquorice extract has mineralocorticoid-like effects and can cause hypokalaemia, hypertension, cardiac arrhythmia and myopathy.
- Patients taking fludrocortisone or medicines which can deplete potassium should avoid eating liquorice or taking supplements containing liquorice extract.

The Centre for Adverse Reactions Monitoring (CARM) recently received a report of a man taking fludrocortisone who experienced very high blood pressure and panic attack (CARM ID: 133830). He had been taking fludrocortisone for a long period without problem. During assessment in hospital, the patient recalled that he had recently started eating liquorice.

Liquorice extract has mineralocorticoid-like effects

Liquorice (or licorice) extract is derived from the plant *Glycyrrhiza glabra*. Liquorice extract is used as a sweetener and as a flavouring agent in sweets and is also marketed as a dietary supplement¹.

Liquorice extract contains the compound glycyrrhizin. The active metabolites of glycyrrhizin, glycyrrhizic acid and glycyrrhetic acid, inhibit the metabolism of cortisol and bind to the mineralocorticoid receptor giving liquorice its mineralocorticoid-like activity¹. (Note that some liquorice sweets may be flavoured with anise oil instead of liquorice extract; anise oil does not contain glycyrrhizin.)

Potential side effects

Liquorice extract consumption can reduce blood potassium levels resulting in abnormal heart rhythms, high blood pressure, oedema, lethargy, heart failure and hypokalaemic myopathy manifesting as flaccid paralysis¹⁻³. In general, an upper limit of 100mg/day glycyrrhizin is recommended, which approximates to 60 to 70g of liquorice sweets¹.

Liquorice overconsumption should be suspected in people presenting with otherwise unexplained hypokalaemia and muscle weakness. The cortisol:cortisone ratio in the peripheral venous plasma is raised and there is a reduction in plasma renin and aldosterone level¹.

Sensitivity to glycyrrhizin is increased by prolonged gastrointestinal transit time, hypertension, and old age, and is more common in females¹.

Potential liquorice interactions

Pharmacodynamic interactions are possible with liquorice and fludrocortisone due to mineralocorticoid effects, and with liquorice and medicines that deplete potassium levels such as diuretics. Patients taking these medicines should avoid regular consumption of liquorice.

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Test your knowledge: The Prescriber Update Quiz 2019

Have you been reading Prescriber Update in 2019?

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 93 or at www.medsafe.govt.nz/profs/PUPDF.asp

- 1. Paraffin-based emollients are flammable.**
True False
- 2. In general, it is safe to consume how much liquorice per day?**
a) 10 g b) 60 g c) 200 g d) more than 200 g
- 3. Hepatotoxicity is a significant risk of harm with vildagliptin. Liver function tests should be performed:**
a) before starting treatment, and as required if symptoms of liver toxicity occur
b) before starting treatment and once during the first year of treatment
c) before starting treatment and once per year for the first two years of treatment
d) before starting treatment, at 3-monthly intervals during the first year of treatment, and periodically thereafter
- 4. What is the term for the clump of tablets in the gut which may be seen after very large overdoses of modified-release paracetamol?**
- 5. Who is responsible for the content of data sheets and consumer medicine information?**
a) Pharmaceutical companies b) Medsafe c) PHARMAC d) All of the above
- 6. Approximately how much of the active ingredient included in an eye drop reaches the systemic circulation?**
a) 10 percent b) 50 percent c) 80 percent d) 100 percent
- 7. In healthy adults, the elimination half-life of zopiclone after a single dose is 5 hours. Approximately how much longer is it in patients with hepatic failure?**
a) no longer b) 3 hours c) 5 hours d) 7 hours
- 8. Low-dose vitamin K is an anticoagulant reversal agent for rivaroxaban.**
True False
- 9. The requirements for a valid adverse drug reaction report are:**
a) suspect medicine, one patient identifier, reporter details
b) one patient identifier, suspect medicine, suspected reaction, reporter details
c) suspected reaction, suspect medicine, reporter details, patient's name and date of birth
d) reporter details, patient's name and date of birth, suspected reaction
- 10. Some medicines have been associated with bullous pemphigoid. Name three of them.**

Medicinal Cannabis Scheme: Update from the Ministry of Health

The Medicinal Cannabis Scheme (the Scheme) is being established to meet the Government's commitment to increase access to medicinal cannabis products.

Under the Scheme, medicinal cannabis products will only be available as prescription medicines, prescribed by a medical practitioner. This includes both cannabidiol (CBD) products and products containing tetrahydrocannabinol (THC), the psychoactive component of cannabis.

The Ministry is currently working on the regulations required to support the Scheme. The regulations will include:

- a licensing regime for the cultivation of cannabis
- a licensing regime for the manufacture and supply of medicinal cannabis products
- a requirement for medicinal cannabis products imported into or manufactured in New Zealand to meet minimum standards of quality.

Compliance with quality standards will give medical practitioners, as well as consumers and potential export markets, confidence that the medicinal cannabis products contain, for example, consistent amounts of specified ingredients, and have limits on contaminants such as pesticides or mould.

The regulations that set the minimum quality standards will be made by 18 December 2019 and the Scheme will commence in the first quarter of 2020. Medicinal cannabis products will be required to meet the quality standards once the Scheme commences. Medicinal cannabis products which are available now will also be required to meet the quality standards, but there will be a transition period after commencement for such products to be submitted to the Ministry for assessment.

As mentioned in the September update, most medicinal cannabis products available under the Scheme are likely to be 'unapproved' products (www.medsafe.govt.nz/profs/PUArticles/September2019/Medicinal-Cannabis-Scheme-Update.htm). These products cannot be advertised but the Ministry will make available to prescribers a list of unapproved medicinal cannabis products that meet the quality standards. This list will be available after the Scheme commences, and once products have been assessed.

More information

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

Aortic aneurysm/dissection – The Achilles heel of fluoroquinolones

Key messages

- Aortic aneurysm and dissection have recently been linked to fluoroquinolone treatment.
- People at risk of aortic aneurysm and dissection include those with a family history of aneurysm, pre-existing aortic aneurysm and/or dissection, genetic predisposition, atherosclerosis, hypertension and advanced age.
- Avoid using fluoroquinolones in people at risk of aortic aneurysm and dissection.

Fluoroquinolones, including ciprofloxacin, norfloxacin and moxifloxacin, are associated with an increased risk of aortic aneurysm and aortic dissection.

What is aortic aneurysm and dissection?

Aortic aneurysm is a localised or diffuse dilation of the aorta, while aortic dissection occurs when there is separation of the layers within the aortic wall¹. These conditions are associated with alterations in collagen content, concentrations and structure.

Tendon rupture is known to occur with fluoroquinolone treatment. The aorta contains the same type of collagen as the Achilles tendon. Therefore, fluoroquinolones may degrade the collagen along the aortic wall in a similar way to the collagen in tendons and, as such, contribute to progression or rupture of an aneurysm¹⁻³. However, the exact mechanism is not known²⁻⁴.

About the risk

The Medicines Adverse Reactions Committee (MARC) discussed the risk of aortic aneurysm and dissection associated with fluoroquinolones at the June 2019 meeting⁵. Data from recent observational studies and overseas case reports indicate patients taking fluoroquinolones have about a two-fold increase in risk in compared with patients taking no antibiotics or other antibiotics (eg, amoxicillin)²⁻⁴.

The annual background risk varies in the literature between 3 and 20 per 100,000 population, and up to 300 per 100,000 among the oldest or for people with other risk factors⁶⁻⁷. Risk factors include a family history of aneurysm disease, pre-existing aortic aneurysm and/or aortic dissection and atherosclerosis.

New Zealand reports

Up to 31 March 2019, the Centre for Adverse Reactions Monitoring (CARM) had not received any local reports of aortic aneurysm or dissection associated with fluoroquinolone use.

Regulatory action

Regulators overseas have issued warnings about the risk of aortic aneurysm and dissection associated with fluoroquinolones. Medsafe is currently working with the manufacturers of fluoroquinolones to include a similar warning in the New Zealand data sheets.

Advice for healthcare professionals

For prescribers: if patients have risk factors for aneurysm or dissection, only prescribe fluoroquinolones after careful benefit-risk assessment and after consideration of other therapeutic options.

For cardiologists and vascular surgeons: please provide information/advice to the general practitioner if screening shows a patient has the potential for developing an aneurysm or dissection⁵.

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Some medicines increase serum creatinine without affecting glomerular function

Key messages

- Medicines that interfere with the active secretion of creatinine can increase the serum creatinine level without affecting glomerular function.
- Trimethoprim may cause a reversible increase in serum creatinine due to inhibition of cellular transporter proteins in the proximal tubule.
- Consider reversible inhibition of active secretion as a possible cause for an elevated serum creatinine in patients taking trimethoprim.

Inhibition of active secretion in proximal tubule

Creatinine is a waste product that is formed during normal muscle catabolism. It is removed from the blood by the kidneys, primarily by glomerular filtration. An increase in serum creatinine usually reflects a reduction in glomerular function.

A small proportion (approximately 15 percent) of creatinine is actively secreted into the urine by the proximal tubule. Inhibition of transporter proteins located in the proximal tubule cell membrane can result in an elevated serum creatinine level and a corresponding fall in the creatinine clearance, without affecting glomerular function^{1,2}.

In patients with impaired glomerular filtration, a greater proportion of creatinine is excreted via active secretion. Inhibition of the transporter proteins in the proximal tubule cell membrane may have a more significant effect on serum creatinine in patients with chronic kidney disease (CKD), compared to individuals with normal glomerular function².

Medicines that interfere with active secretion of creatinine

Some medicines interfere with the active secretion of creatinine through competition for certain transporter proteins in the proximal tubule cell membrane.

Trimethoprim is one such medicine known to inhibit the secretion of creatinine in the proximal tubule^{1,3}.

Other currently approved medicines that have been reported to compete with the active secretion of creatinine include amantadine⁴, cobicistat⁵ and olaparib⁶.

The increase in serum creatinine is usually reversible on stopping the medicine concerned.

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Report vaping side effects

There has been some recent media coverage of vaping causing harm, including serious lung illness and deaths reported in the United States¹ and elsewhere. The Ministry of Health continues to monitor new research and developments. To date, there are no signs of similar concerns in New Zealand.

To help monitor vaping safety in New Zealand, the Centre for Adverse Reactions Monitoring (CARM) has developed an online vaping reporting form. Anyone who suspects that a vaping product has caused harm can report it to CARM at:

<https://nzphvc.otago.ac.nz/report-vaping/>

As with adverse drug reaction reports made to CARM, all vaping reports are confidential. Any information that is shared with government departments to monitor vaping safety will be anonymised.

For more information about vaping, see Vaping Facts (vapingfacts.health.nz).

Reference

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Quiz answers

1. **False.** Paraffin-based emollients are not themselves flammable. Clothing, bedding or medical dressings covered in paraffin-based emollients are at risk of catching fire and are the main hazard. (June 2019)
2. **b.** It's safe to consume 60–70 g of liquorice per day. (December 2019)
3. **d.** Liver function tests should be performed before starting treatment with vildagliptin, at 3-monthly intervals during the first year of treatment, and periodically thereafter. (September 2019)
4. **A pharmacobezoar.** With very large overdoses, the modified-release paracetamol tablets may form a clump (called a pharmacobezoar) in the gut, which can further delay absorption due to altered disintegration and dissolution properties of the clumped tablets. (March 2019)
5. **a.** Pharmaceutical companies are responsible for the content of data sheets and CMI, including keeping the information up-to-date. (September 2019)
6. **c.** It is estimated that only 5–10 percent of the active medicine included in an eye drop remains in the eye, and up to 80 percent may reach the general circulation. (December 2019)
7. **d.** In patients with hepatic failure, the elimination half-life of zopiclone is prolonged to nearly 12 hours (so is 7 hours longer than in healthy adults). (June 2019)
8. **False.** There is no anticoagulant reversal agent for rivaroxaban. (March 2019)
9. **b.** The four requirements for a valid adverse drug reaction report are: one patient identifier (eg, name, initials, gender, date of birth, age), suspect medicine, suspected reaction, reporter details. (June 2019)
10. Bullous pemphigoid has been associated with penicillamine, furosemide, captopril, penicillin and its derivatives, sulfasalazine, topical fluorouracil, neuroleptics, loop diuretics, spironolactone, dipeptidyl peptidase inhibitors (eg, vildagliptin, sitagliptin, saxagliptin). (March 2019)

Medsafe

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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 Eng, Manager Regulatory Practice and Analysis

Andrea Kerridge, Senior Advisor Pharmacovigilance

Ben Jones, Team Leader Medicines Assessment

Dr Geraldine Hill, Senior Medical Advisor

Jo Prankerd, Senior Advisor Pharmacovigilance

Lily Chan, Principal Technical Specialist Pharmacovigilance

Maria Storey, Senior Advisor Pharmacovigilance

Dr Tina Ireland, Medical Advisor

Dr Susan Kenyon, PhD, Manager Clinical Risk

Acknowledgement

Dr David Chinn, Hutt Valley DHB

Associate Professor David Menkes, University of Auckland

Associate Professor David Reith, University of Otago

Dr Hiran Thabrew, University of Auckland

Dr Matt Eggleston, Canterbury DHB

Dr Michael Tatley, Centre for Adverse Reactions Monitoring

Dr Ruth Savage, Centre for Adverse Reactions Monitoring

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Clinical Advisor Dr Geraldine Hill **Group Manager** Chris James

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