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Contents

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Spotlight on lisdexamfetamine

Key messages

- Lisdexamfetamine is a stimulant medicine used for the treatment of attention deficit hyperactivity disorder (ADHD) in children aged 6 years and over and adults.
- Stimulants, including lisdexamfetamine, may be associated with abuse, cardiovascular effects, new or worsening symptoms of psychiatric disorders, appetite suppression, growth suppression (in children) and blurred vision.
- There is a risk of serotonin syndrome when stimulants such as lisdexamfetamine are used with other serotonergic medicines.

This article gives an overview of lisdexamfetamine (Vyvanse), a medicine newly available in New Zealand for the treatment of attention deficit hyperactivity disorder (ADHD).

Indications and mechanism

Lisdexamfetamine is indicated for the treatment of ADHD in children aged 6 years and older and adults as part of a comprehensive treatment programme.[1] Since it is a class B2 controlled drug, there are restrictions on prescribing, supplying and administering lisdexamfetamine.[2] A paediatrician or psychiatrist should initiate treatment.[3]

Lisdexamfetamine is an inactive prodrug of dexamfetamine, a central nervous system stimulant. It has an extended duration of action and is taken once daily.[1]

The therapeutic mechanism of both lisdexamfetamine and dexamfetamine is not fully understood. However, dexamfetamine blocks the reuptake of noradrenaline and dopamine into the presynaptic neuron and increases the release of these monoamines into the extraneuronal space.[1]

Considerations for use

Monitoring of treatment response

Start lisdexamfetamine at the lowest possible dose and titrate slowly to the lowest effective dose.[1]

Regularly review patients for adverse effects, response to treatment and whether there is an ongoing need for treatment.[1,4,5]

Treatment non-response can be related to dose, timing or choice of medicine.[6] Discuss partial or non-response to any ADHD medicine with a specialist clinician.

Most individuals with ADHD have co-morbid conditions that complicate the clinical presentation and may also affect the treatment response to lisdexamfetamine and other medicines.[6] Examples include substance abuse, comorbid affective disorders such as major depression or anxiety disorders, sleep disorders such as obstructive sleep apnoea, post-traumatic stress disorder (PTSD) and thyroid disorders.[6]

Cardiovascular risk

Stimulant medicines may increase blood pressure and heart rate. These changes are usually minor but may be more significant in individual patients. Lisdexamfetamine is contraindicated in patients with symptomatic cardiovascular disease.

Before starting treatment, evaluate patients for cardiac risk factors, including family history. Regularly review blood pressure and cardiovascular status during treatment.[1]

See the lisdexamfetamine data sheet and ADHD treatment guidelines for more information about managing cardiovascular risk.

Abuse and dependence

Amphetamines have abuse potential and may cause psychological dependence. Lisdexamfetamine should not be used in patients with known drug or alcohol dependence or a history of methamphetamine or stimulant abuse. Assess the risk of abuse before prescribing and monitor for signs of abuse and dependence during treatment.[1]

Adverse effects

The most frequently reported adverse reactions with lisdexamfetamine include insomnia, gastrointestinal symptoms, anxiety, decreased appetite and headache.[1]

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

Serotonin syndrome

Lisdexamfetamine may cause serotonin syndrome when used with other serotonergic medicines or in overdose.[1]

Tourette's syndrome

Stimulants may exacerbate tics and Tourette's syndrome. Lisdexamfetamine is contraindicated in patients with these conditions.[1]

Psychiatric disorders

Stimulants may exacerbate pre-existing psychotic disorders and bipolar disorder. In children and adolescents, stimulants can cause new psychotic or manic symptoms, aggression or hostility. Monitor patients for the appearance or recurrence of these conditions.[1]

See also the article about unexplained mood and behavioural changes on page 5 of this edition of *Prescriber Update*.

Seizures

Stimulants may lower the seizure threshold. If seizures occur, discontinue treatment.[1]

Growth and appetite suppression

Short-term studies show reduced appetite and weight reduction in adults and children during treatment with lisdexamfetamine. Long-term use of stimulants has been associated with growth suppression in children. Discontinue lisdexamfetamine if the patient is not growing or gaining weight as they should.[1]

Visual disturbance

Stimulants may cause difficulties with accommodation and blurred vision.[1] Monitor the patient for any changes in vision after starting treatment.[7]

More information

For more information on ADHD treatment options, refer to local clinical guidelines. Other resources include:

- lisdexamfetamine (Vyvanse) New Zealand data sheet
- United Kingdom National Institute for Health and Care Excellence (NICE) ADHD management guideline
- Canadian ADHD Resource Alliance (CADDRA) practice guidelines.

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Medicines Monitoring: DPP-4 inhibitors and possible risk of ileus

WE NEED YOUR HELP!

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

Medicine(s)	Potential safety issue	Active monitoring ends
DPP-4 inhibitors	Ileus	15 June 2024

- 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/Medsafe (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.

Unexplained mood and behavioural changes – could it be a side effect?

Key messages

- Some non-psychotropic medicines can cause psychiatric side effects such as changes in mood and behaviour.
- Very old and very young patients and those with past or present psychiatric disorders may be more susceptible to psychiatric side effects.
- Advise patients and their whānau or caregivers to seek medical advice if they notice any changes in mood or behaviour when starting medicines with psychiatric effects.
- Consider medicine side effects as part of the differential diagnosis in people presenting with new or worsening psychiatric symptoms.

Medicines can cause psychiatric side effects, including mood and behavioural changes.[1]

This article highlights the psychiatric side effects of non-psychotropic medicines frequently prescribed in primary care settings.

Medicines with psychiatric side effects

Psychiatric side effects of medicines are defined as new psychiatric symptoms that develop during treatment or worsening of pre-existing psychiatric disorders.[1] In some cases, symptoms may also occur on withdrawal of a medicine.[2]

Side effects may resemble symptoms associated with psychiatric disorders, such as agitation, euphoria, confusion, delusional thoughts, hallucinations, low mood and depression.[2]

Risk factors that may predispose patients to develop psychiatric side effects with medicines include present or past history of psychiatric disorders, extremities of age (very young or very old) and higher doses.[2]

Table 1 provides examples of medicines (excluding psychotropics) where the data sheets list psychiatric side effects as known adverse reactions. Note: Table 1 is not a complete list of all medicines and adverse reactions.

Table 1: Examples of medicines (excluding psychotropic medicines) that can cause psychiatric side effects

Medicine class	Examples of medicine(s)	Examples of psychiatric side effects listed in data sheet
ACE inhibitors	Enalapril, quinapril	Depression, confusion, insomnia
Antivirals	Aciclovir, valaciclovir	Confusion, hallucinations, agitation, psychotic disorder
Antibiotics	Sulfamethoxazole + trimethoprim	Depression, hallucination, psychotic disorder, insomnia, apathy, mental depression, hallucinations
	Metronidazole	Psychotic disorder, confusion, hallucinations, depression, insomnia, irritability
	Rifampicin, isoniazid	Psychotic disorder
Anticholinergic	Oxybutynin	Agitation, anxiety, hallucinations, nightmares, paranoia, depression, confusion, behavioural disorders
	Hyoscine hydrobromide	Confusion, hallucinations
Antihistamines	Cetirizine	Agitation, aggression, confusion, depression, hallucination, insomnia, tic, suicidal ideation, nightmare
	Promethazine	Euphoria, excitation, catatonic-like states, hysteria, agitation, confusional states
Beta-blockers	Metoprolol, bisoprolol	Depression, hallucinations, insomnia, nightmares
Calcium channel blockers	Amlodipine, diltiazem	Mood changes
Cardiac glucosides	Digoxin	Depression, psychotic disorder, apathy, confusion
Combined oral contraceptives	Levonorgestrel + ethinylestradiol Norethisterone + ethinylestradiol	Depressed mood, altered mood
Corticosteroids	Prednisone, dexamethasone	Euphoria, depression, mania, delusions, hallucinations, insomnia, suicidal ideation
Leukotriene receptor antagonists	Montelukast	Nightmares, agitation, depression, psychomotor hyperactivity, hallucinations, obsessive-compulsive symptoms, suicidal behaviour
Proton pump inhibitors	Omeprazole, pantoprazole	Agitation, confusion, depression, hallucinations

Continues

Medicine class	Examples of medicine(s)	Examples of psychiatric side effects listed in data sheet
Other	Isotretinoin	Depression, behavioural disorders, suicidality
	Tacrolimus	Insomnia, confusion, depression, mood disorders, mood disturbances, nightmare, hallucination, psychiatric disorder

Note: This table is not a complete list of all medicines and adverse reactions.

Source: Medsafe data sheets and consumer medicine information search. URL: www.medsafe.govt.nz/Medicines/infoSearch.asp (accessed 11 January 2024).

Advise patients, whānau and caregivers about psychiatric side effects

When starting medicines with known psychiatric side effects, advise patients and their whānau and/or caregivers about possible signs and symptoms and what to do if these occur.

Whānau, friends and caregivers can play an important role in alerting patients to possible changes in their mood and/or behaviour.

Advise parents and/or caregivers to closely monitor young children, including asking the child about possible side effects.

Psychiatric side effects may be difficult to identify

Consider medicine side effects as part of the differential diagnosis in patients presenting with new or worsening psychiatric symptoms.[3]

It may be challenging to establish if the symptoms are medicine-related.[3] Consult the medicine data sheet to check if psychiatric effects are known to be associated with the suspected medicine.

One or more of the following features may suggest a medicine-related effect:[3]

- a temporal relationship between medicine exposure and side effect
- positive de-challenge (symptoms improve after stopping the medicine)
- positive re-challenge (symptoms recur after restarting the medicine).

Psychiatric side effects are generally reversible after discontinuation of the suspected medicine.[3]

Further information

Healthify: Medicines that affect mood

Previous *Prescriber Update* articles:

- Inhaled and systemic corticosteroids and mood disorders (June 2016)
- Oxybutynin – Psychiatric side effects (March 2017)
- Montelukast – Reminder about neuropsychiatric reactions (September 2017)

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Medicine safety reminder: avoid unintentional poisoning in the home

Key messages

- Some medicines can be highly toxic to people or pets, even in small amounts.
- Young children are at particular risk of unintentional poisoning from medicines.
- Consider safe prescribing strategies when prescribing medicines that are known to be harmful when used inappropriately.
- Remind patients to:
  - keep all medicines out of sight ***and*** reach of children and pets
  - never share prescription medicines.

Substances found around the house, including medicines, are common causes of unintentional poisoning in children and pets.[1,2] About 20 percent of families with pre-school age children experience a poisoning every year.[3] However, it is important to remember that people of any age can be poisoned by medicines found in the home.[4]

Medsafe is also aware of fatal cases of poisoning from fluorouracil (5-FU) cream in pets in New Zealand and overseas.[5] The New Zealand data sheet and consumer medicine information (CMI) for Efudix were recently updated with animal safety advice.[6,7]

General considerations

The risks associated with a poisoning will depend on several factors relating to the medicine (eg, the type and quantity of the medicine involved, the route of exposure) and individual characteristics such as age, weight, medical history.[8–10]

While most exposures are unlikely to have serious outcomes, some medicines can cause serious toxicity or death, even in very small amounts.[9–11]

Poisoning in children

More than half of calls to the New Zealand National Poisons Centre relate to children aged under 5 years, and children aged 1 to 3 years are the most likely age group to be poisoned. This includes poisoning from household chemicals and medicines.[1]

Table 1 lists some of the medicines most commonly reported to the National Poisons Centre for poisonings in children aged under 5 years.

Table 1: Examples* of medicines most commonly reported in poisonings of children aged under 5 years

Paracetamol	Anti-inflammatories	Thyroid medicines
Multivitamins	Antihistamines	Antibiotics
Oral contraceptives	Cold and flu medicines	

* Not an exhaustive list.
Source: National Poisons Centre. *Facts about childhood poisoning*. URL: poisons.co.nz/articles-and-info/poisoning-issues-specific-to-young-children/view/facts-about-childhood-poisoning/ (accessed 15 January 2024).

Table 2 provides some examples of medicines that can cause significant toxicity in children in small amounts (one or two tablets).[9]

Table 2: Examples* of medicines that can cause significant toxicity in children in small amounts (one or two tablets)

Class	Examples
Calcium channel blockers	Diltiazem, verapamil
Opioids	Morphine, fentanyl
Tricyclic antidepressants	Amitriptyline, nortriptyline
Sulfonylureas	Glipizide, gliclazide
Anti-gout medicines	Colchicine

* Not an exhaustive list.
Source: bpac^{NZ}. 2022. *Childhood poisonings: hazardous substances around the home* November 2022. URL: bpac.org.nz/2022/docs/hazardous.pdf (accessed 15 January 2024).

Poisoning in pets

Pets metabolise many medicines differently from humans.[12] Some medicines commonly used in humans are highly toxic to pets, for example, anti-inflammatories, paracetamol, cold and flu medicines, antihistamines, antidepressants and vitamins.[2,11,12]

Topical medicines (such as creams and ointments) can also be harmful when ingested by pets, including by licking if off the skin. Those containing 5-FU, calcipotriol or minoxidil are particularly harmful, even in small amounts.[13]

Safety advice

Consider safe prescribing strategies when prescribing medicines that are known to be harmful when used inappropriately.[14]

Remind patients to:

- keep all medicines out of sight ***and*** reach of children and pets
- never share prescription medicines
- store medicines in their original containers and separately from food
- put medicines away immediately after use
- not rely on child-resistant caps (they are not child-proof)
- safely dispose of old or unused medicines by returning them to the pharmacy.[15,16]

In addition, remind patients using topical medicines to:

- avoid letting pets contact or lick the container or the skin where the medicine was applied
- wash hands thoroughly after using
- safely discard or clean any items (eg, cloths, applicators, clothing) that may contain medicine residue.[6,13]

More information

Medicine safety

- Medsafe: Taking medicines safely
- Healthify: Medicine – safety tips

Medicines

For more information about a particular medicine, see the data sheet and consumer medicines information (CMI): Search for a data sheet or CMI.

Poisons

For information about poisons or in case of child or pet poisoning, call:

- New Zealand National Poisons Centre, free phone 0800 POISON (0800 764 766)
- Animal Poisons Helpline, free phone 0800 TOX PET (0800 869 738).

Or seek advice from a health professional or vet.

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Quarterly summary of recent safety communications

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

Date	Communication	Topic
04/03/2024	Alert	Recent cases of lead poisoning with Ayurvedic Medicines
25/01/2024	Dear Healthcare Professional Letter	Paxlovid (nirmatrelvir + ritonavir) – pack changes, updated contraindications, dosing (PDF, 7 pages, 630 KB)
24/01/2024	Consumer leaflet	Epilepsy medicines and pregnancy (Te Reo version) (PDF, 2 pages, 569 KB)
23/01/2024	Media release	Medsafe successfully prosecutes seller of fake "Miracle Cure"
15/01/2024	Monitoring	DPP-4 inhibitors and the possible risk of ileus
29/12/2023	Consumer leaflet	New labelling requirements for excipients (PDF, 2 pages, 157 KB)
12/12/2023	Consumer leaflet	Epilepsy medicines and pregnancy (PDF, 2 pages, 271 KB)
07/12/2023	Alert	Update – Sodium valproate (Epilim) use in people who can father children: important new safety information
28/11/2023	Dear Healthcare Professional Letter	Epilim (valproate) – Potential risk to children of fathers treated with valproate: update (PDF, 2 pages, 179 KB)
28/11/2023	Committees	Update – Reclassification of methenamine hippurate

Pharmacokinetic changes in pregnancy and effects on antiepileptic medicine plasma levels

Key messages

- Physiological changes during pregnancy can affect the absorption, distribution, metabolism and elimination of medicines. This may influence the plasma levels of antiepileptic medicines during pregnancy.
- The relationship between declining plasma antiepileptic medicines levels in pregnancy and deterioration in seizure control is not well characterised.
- Therapeutic drug monitoring of antiepileptic medicines may be useful in some cases and dose adjustments may be needed.

This article provides an overview of the pharmacokinetic changes in pregnancy, their effects on antiepileptic medicine (AEM) plasma levels, and therapeutic drug monitoring considerations. Due to the risks to the fetus, as well as the potential need to monitor medicine levels, all pregnancies should be planned.

Pharmacokinetic changes during pregnancy

Physiological changes during pregnancy can affect the absorption, distribution, metabolism and elimination of medicines. This may influence the plasma levels of AEMs during pregnancy.[1]

Absorption

During pregnancy, the gastric pH increases (becomes less acidic) while gastric emptying and intestinal motility decreases.[1] For most medicines, there is no significant clinical effect as a result of these changes.[2]

Distribution

The plasma volume and total body water increases during pregnancy. This in turn can lower the plasma concentration of hydrophilic medicines.[3]

Plasma protein concentrations also fall during pregnancy, which can result in decreased plasma protein binding of medicines. For example, albumin concentrations decrease on average by 1% at 8 weeks gestation, 10% at 20 weeks, and 13% at 32 weeks[3]. The total plasma concentration of highly protein bound medicines may decrease in parallel with albumin levels.[1]

Metabolism

The activity of enzymes involved in drug metabolism may change during pregnancy. Certain cytochrome P450 (CYP450) enzyme activities may increase (eg, CYP3A4 and CYP2D6) or decrease (eg, CYP2C19) and uridine glucuronyl transferase (UGT) enzyme activity increases. Therefore, the plasma levels of a medicine may increase or decrease during pregnancy, depending on the hepatic enzymatic process involved in its metabolism.[2]

Excretion

Blood flow and glomerular filtration rate (GFR) increase during pregnancy, leading to increased renal clearance.[1] For medicines that are primarily renally cleared, renal clearance is expected to parallel changes in GFR.[3]

Plasma levels of antiepileptic medicines may change during pregnancy

Pregnancy may reduce maternal AEM plasma levels. This reduction varies depending on the type of AEM and between individuals.[1] A projected decrease in serum concentration for some AEMs (if no dose changes are made) and possible pharmacokinetic mechanisms described in the literature are outlined in Table 1.

Table 1: Projected changes in serum concentrations of selected antiepileptic medicines during pregnancy (if no dose changes are made) and possible mechanisms

Antiepileptic medicine	Decrease in serum concentration[a]	Examples of possible pharmacokinetic mechanisms described in the literature (list not exhaustive)
Phenobarbital	Up to 55%	Altered protein binding[b]
Phenytoin	60 to 70%	Altered protein binding[c]
Carbamazepine	0 to 12%	Not well described[d]
Oxcarbazepine monohydrate-derivative	36 to 62%	Enhanced hepatic metabolism[d] Increased renal clearance[d]
Sodium valproate	Up to 23%	Altered protein binding[c]
Lamotrigine	69% decrease in 77% of population[e] 17% decrease in 23% of population[e]	Uridine glucuronyl transferase enzyme upregulation[d] Increased renal clearance[d]
Gabapentin and pregabalin	Insufficient data	Increased renal clearance[d]
Topiramate	Up to 30%	Increased renal clearance[d]
Levetiracetam	40 to 60%	Increased renal clearance[d]
Zonisamide	Up to 35% but little data	Reduced gastrointestinal absorption[d] Enhanced hepatic metabolism[d] Increased renal clearance[d]

Notes:

a. Adpated from McElrath T and Gerard E. 2023. Management of epilepsy during preconception, pregnancy, and the postpartum period. In: *UpToDate* 23 October 2023. URL: www.uptodate.com/contents/management-of-epilepsy-during-preconception-pregnancy-and-the-postpartum-period (accessed 10 January 2024).

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e. A pharmacokinetic analysis utilising a population-based model demonstrated two subpopulations based on the rate of lamotrigine clearance during pregnancy. Most women (77 percent) displayed a marked increase in lamotrigine clearance (ie, a decrease in serum concentration) from baseline, whereas a minority (23 percent) had a minimal decrease (Source: McElrath and Gerard, see note a above).

Considerations for therapeutic drug monitoring in pregnancy

The relationship between changes to plasma AEM levels in pregnancy and deterioration in seizure control is not well characterised, and pregnant patients may remain seizure free despite lower AEM levels. However, therapeutic drug monitoring may be useful in some cases and dose adjustments may be needed.[1] Seek specialist advice.

The New Zealand Formulary recommends dose adjustments during pregnancy based on therapeutic drug monitoring for phenytoin, carbamazepine and lamotrigine.[4] The dose of levetiracetam may need to be increased in the second and third trimesters.[4] Carefully monitor the dose of other AEMs during pregnancy and adjust if clinically needed.[4]

To aid clinical decision making during pregnancy, it may be useful to establish baseline AEM plasma levels as part of pregnancy planning.[5,6] This level may then be used to compare and titrate against when AEMs levels are measured during pregnancy.[7]

The optimal frequency for therapeutic drug monitoring of AEMs during pregnancy is unknown.[5] Some guidelines recommend monitoring every trimester or more frequently if seizures occur.[8]

Additional information

For prescribers

- Refer to the medicine data sheet and local clinical guidance.

For patients

- Refer to the consumer medicine information or package leaflet for your medicine.
- See also Medsafe's *Epilepsy medicines and pregnancy* consumer information leaflet – available in English (PDF, 2 pages, 271 KB) and te reo Māori (PDF, 2 pages, 569 KB).

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Interacting safely with low-dose methotrexate

Key messages

- Low-dose methotrexate is used in the treatment of autoimmune conditions, such as psoriasis and rheumatoid arthritis, often in patients taking other medicines.
- Use of methotrexate with some medicines may increase the risk of methotrexate side effects and toxicity.
- Consider possible medicine interactions and their appropriate management when starting or changing doses of medicines in patients taking low-dose methotrexate.

Low-dose methotrexate in weekly doses is used as an immunosuppressant to treat conditions such as psoriasis and rheumatoid arthritis. Patients taking low-dose methotrexate may need to take other medicines for long-term conditions or when acutely unwell.

Taking methotrexate with some medicines may increase the risk of methotrexate side effects and toxicity. This article describes some of these interactions.

Characteristics of interactions[1,2]

Methotrexate is a cytotoxic medicine that inhibits the enzyme dihydrofolate reductase, thereby interfering with folic acid metabolism. Additive toxicity may occur if methotrexate is used with medicines with similar pharmacological effects.

Methotrexate, even at low doses, can cause bone marrow suppression and renal, hepatic, gastrointestinal or pulmonary toxicity. Elevated plasma concentrations of methotrexate may increase the risk of toxicity.

Methotrexate is partly bound to serum albumin following absorption. Concomitant use with medicines competing for the same albumin binding site or inhibiting albumin binding may displace methotrexate, increasing plasma concentrations.

Methotrexate is almost completely excreted through the kidneys by glomerular filtration and active transport. Medicines that affect renal function or renal tubular transport may reduce the clearance of methotrexate, thereby increasing plasma concentrations.

Examples of interactions

Table 1 provides some examples of interactions with methotrexate, showing the effect on methotrexate (increase in plasma levels or pharmacological effect), the mechanism and interacting medicines. Methotrexate can affect other medicines, which are not discussed here. Refer to the methotrexate data sheets for complete information on known interactions.

Table 1: Some examples of interactions increasing methotrexate effects

Effect	Mechanism	Examples of medicines
Increase in methotrexate plasma levels (pharmacokinetic interactions)	Reduced renal clearance of methotrexate	Penicillins and sulfonamides (eg, co-trimoxazole), NSAIDs
	Reduced renal tubular secretion	Probenecid, loop diuretics, ciprofloxacin, NSAIDs
	Protein binding displacement	Sulfonamides, penicillins, tetracyclines, chloramphenicol, salicylates, NSAIDs, sulfonylureas, phenytoin
Increase in methotrexate pharmacological effect (pharmacodynamic interactions)	Additive toxicity (hepatotoxicity)	Hepatotoxic medicines such as azathioprine, sulfasalazine, leflunomide, alcohol, cytotoxic medicines, retinoids
	Additive toxicity (haemotoxicity)	Myelosuppressive medicines such as co-trimoxazole, trimethoprim, leflunomide, allopurinol, ciclosporin, cytotoxic medicines.
	Additive toxicity (other)	Leflunomide (pulmonary toxicity), cytotoxic medicines (pulmonary, gastrointestinal, renal toxicity), amiodarone (ulcerative skin lesions)

Sources: Trexate and DBL Methotrexate Injection New Zealand Data Sheets (accessed 17 January 2024).

Clinical considerations

When starting a new medicine in a patient taking methotrexate, consider whether the medicine may affect the kidneys or liver or cause blood disorders. Depending on the situation, the methotrexate dose may need to be adjusted or doses withheld. An increase in monitoring may be required.[1–3]

Advise patients to:

- watch out for signs of potential toxicity and what to do if these occur
- check with a healthcare professional before taking any over-the-counter medicines, including natural health products.[3]

New Zealand case reports

Since 2020, there have been five cases of drug interactions with low-dose methotrexate. The medicines involved in these reports were co-trimoxazole (2 cases), trimethoprim, amoxicillin + clavulanic acid, and aspirin and sodium valproate.

The amoxicillin + clavulanic acid case reported deranged liver function tests following four doses of amoxicillin + clavulanic acid. These data sheets are being updated to include an interaction with methotrexate.

More information

See also the following *Prescriber Update* articles for more information about the New Zealand case reports and/or interactions.

- Gathering knowledge from adverse reaction reports: June 2020
- Interaction reminder: Bone marrow suppression with methotrexate and trimethoprim or co-trimoxazole
- Administration of methotrexate in individuals taking sodium valproate may reduce seizure or mood control

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Recent approvals: new active ingredients or new indications

New active ingredients

Table 1 shows recent approval of medicines with new active ingredients gazetted during the period 13 October 2023 to 1 February 2024.

Table 1: Recent approvals of medicines with new active ingredients

Medicine	New active ingredient[a]	Dose form: strength(s)	Therapeutic area
Verzenio	Abemaciclib	Film coated tablet: 50mg, 100mg, 150mg	Breast cancer (hormone receptor [HR] positive, human epidermal growth factor receptor 2 [HER2] negative)
Ryeqo 40/1/0.5	Relugolix	Film coated tablet: 40mg/1mg/0.5mg	Uterine fibroids
Tukysa	Tucatinib	Film coated tablet: 50mg, 150mg	Breast cancer (HER2 positive)
Comirnaty Omicron XBB 1.5	Raxtozinameran	Suspension for injection: 0.1mg/mL	COVID-19 prevention
Tremfya	Guselkumab	Solution for injection (pen and syringe): 100mg/mL	Adults with plaque psoriasis or psoriatic psoriasis
Vumerity	Diroximel fumarate	Enteric coated capsule: 231mg	Relapsing multiple sclerosis

a. The medicine may also contain other active ingredients

New indications

Table 2 shows approved medicines with new indications for additional therapeutic areas gazetted during the period 13 October 2023 to 1 February 2024.

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

Medicine (active ingredient)	Dose form: strength(s)	New therapeutic area
Jardiance (empagliflozin)	Film coated tablet: 10mg, 25mg	Chronic kidney disease

More information

See the Medsafe website for:

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

Drug-induced phospholipidosis

Key messages

- Drug-induced phospholipidosis (DIPL) can affect any cell or organ in the body. Clinical signs and symptoms of DIPL are non-specific.
- A principal histological feature of DIPL is the accumulation of phospholipids and the inducing medicine/metabolite in affected cells.
- Stopping the suspect medicine usually reverses intracellular changes.

The hydroxychloroquine (Plaquenil) data sheet was recently updated to include warnings for drug-induced phospholipidosis. This article provides information about the disorder.

What is drug-induced phospholipidosis?

Drug-induced phospholipidosis (DIPL) is a lysosomal storage disorder.[1,2] Lysosomes are cellular structures containing enzymes that break down proteins, nucleic acids, carbohydrates and lipids.[3] A phospholipid membrane encloses the lysosome and maintains the acidic environment for the enzymes to function.[3] In lysosomal storage disorders, undegraded material accumulates within the lysosomes of affected individuals.[3]

In DIPL, the inducing medicine causes lysosomal changes that lead to excessive but reversible accumulation of both phospholipids and the medicine in the lysosomes and the formation of lysosomal lamellar bodies.[1,2] They are called lamellar bodies due to the concentric ring shape seen on electron microscopy.[1] Given that nearly all cells contain lysosomes, and phospholipids are found in lysosome membranes, DIPL can affect any cell or organ in the body.[1]

DIPL onset may or may not be associated with clinical symptoms, including inflammatory reactions and histopathological changes, such as macrophagic infiltration or fibrosis.[1,3] DIPL has been associated with organ toxicity, including of the heart, skeletal muscle, liver, lungs and kidneys.[1]

Mechanism

The exact mechanism of DIPL is not known, although there are two hypotheses. The first assumes that the suspect medicine binds directly to phospholipids, creating a drug-lipid complex. The complex then accumulates to form the lysosomal lamellar bodies. The second hypothesis suggests that medicines interact and inhibit phospholipase activity, resulting in an accumulation of phospholipids.[1,4]

Associated medicines

Over 50 medicines are associated with phospholipidosis. Examples of medicines with reports of clinically significant DIPL include:

- amiodarone[1]
- fluoxetine[1]
- gentamicin[1]
- hydroxychloroquine[5]
- perhexiline.[1]

Treat patients presenting with signs and symptoms of organ toxicity as per local clinical guidelines. If DIPL is suspected, discontinue the suspect medicine.

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MARC's remarks: December 2023 meeting

The Medicines Adverse Reactions Committee (MARC) convened on 7 December 2023.

The Committee reviewed the risk of anticoagulant-related nephropathy (ARN) associated with **oral anticoagulants (eg, warfarin, dabigatran, rivaroxaban and apixaban)**. The Committee noted that the risk of haemorrhage from oral anticoagulants is well-known and that ARN is an indirect effect of glomerular haemorrhage. The Committee agreed there was evidence of a class effect and recommended data sheet updates to include ARN.

The Committee reviewed a potential interaction between the use of **estrogen-based hormone replacement therapy (HRT)** and reduction in plasma **lamotrigine** levels. The Committee agreed that, despite limited evidence, there was reasonable biological plausibility to support the interaction. Considering the serious outcomes that may arise from this potential interaction, such as increases in seizure frequency and mood instability, the Committee recommended data sheet updates for estrogen-based HRTs (excluding vaginal preparations).

The Committee reviewed the risk of **tendon disorders** (including tendonitis, tendosynovitis and tendon rupture) with **third-generation aromatase inhibitors (eg, anastrozole, letrozole and exemestane)**. The Committee considered there was sufficient evidence to support a class effect and recommended that the data sheets be updated to include tendon disorders as a warning and adverse event. There was insufficient evidence to support that tendon disorders with third-generation aromatase inhibitors are confined to a specific location.

The Committee reviewed the risk of tumour lysis syndrome (TLS) with **tyrosine kinase inhibitors** and **monoclonal antibodies** when used in cancer treatment. The Committee noted that there is a risk of TLS with any cancer medicine, although the risk depends on the type of cancer and how aggressively the cancer is being treated. The **nivolumab**, **pembrolizumab** and **midostaurin** data sheets do not list TLS. The Committee noted that these medicines are indicated for haematological cancers, which generally have a higher risk of TLS, and recommended data sheet updates to include TLS.

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

Gathering knowledge from adverse reaction reports: March 2024

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

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

Case details[a,b]	Reaction description and data sheet information[b,c]
Report ID: 148910 **Age:** 49 years **Gender:** Male **Medicine(s):** Pregabalin **Reaction(s):** Cognitive disorder, depression, weight increased	The patient experienced cognitive impairment soon after starting treatment with pregabalin. Depression and excessive weight gain were also reported. The symptoms improved with gradual down titration of pregabalin.
	Cognitive disorder (uncommon ADR), depression (common) and weight increased (common) are listed in the Pregabalin Pfizer data sheet.
Report ID: 153033 **Age:** 28 years **Gender:** Female **Medicine(s):** Paracetamol + codeine phosphate **Reaction(s):** Acute pancreatitis	Soon after taking paracetamol + codeine tablets, the patient experienced severe abdominal pains, which was diagnosed as pancreatitis. A few months later, she experienced another episode of pancreatitis soon after taking paracetamol + codeine tablets.
	Pancreatitis is listed as a very rare ADR in the Paracetamol +codeine (Relieve) data sheet.

Continues

Case details[a,b]	Reaction description and data sheet information[b,c]
Report ID: 153818 **Age:** 88 years **Gender:** Male **Medicine(s):** Entacapone **Reaction(s):** Excess sweating	A few days after starting entacapone, the patient experienced profuse sweating. Sweating increased is listed as a common ADR in the Comtan data sheet.
Report ID: 154467 **Age:** Not reported **Gender:** Female **Medicine(s):** Cetirizine **Reaction(s):** Rebound pruritus	The patient experienced intense itching after stopping treatment with cetirizine. The Razene data sheet states that pruritus and/or urticaria may occur when cetirizine is stopped, even if those symptoms were not present before treatment initiation. In some cases, the symptoms may be intense and may require treatment to be restarted. The symptoms should resolve when the treatment is restarted.
Report ID: 154548 **Age:** 79 years **Gender:** Male **Medicine(s):** Nivolumab **Reaction(s):** Myocarditis	The patient developed asymptomatic myocarditis following nivolumab treatment. Immune-mediated myocarditis is a known ADR for Opdivo. Promptly evaluate and closely monitor patients with cardiac or cardiopulmonary symptoms. However, some cases of myocarditis may be asymptomatic. The data sheet also describes treatment modifications according to the severity of the reaction. See also the June 2023 *Prescriber Update* article: Autoimmune complications of immunotherapy.

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, and do not always match the MedDRA term exactly.
c. If the suspect medicine's brand name is not described in the ADR report, only the data sheet for the funded medicine is included in the table.

Information about reported suspected adverse reactions 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).

Recent data sheet updates: important new safety information

Table 1 below provides a list of data sheets recently updated with important new safety information.

Note that this is not a comprehensive list of all recently updated data sheets, nor does it describe all changes to a particular data sheet. To find out if sponsors have made any changes to their data sheets, see Section 10 'Date of revision of the text' (at the end of each data sheet). Search for a data sheet

See also the new and updated data sheets and CMIs page on the Medsafe website.

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

Click on the specific medicine to open the data sheet.

Active ingredient(s): • Medicine(s)	Data sheet updates	
	Section[a]	Summary of new safety information
Cabozantinib • Cabometyx	4.4	Systemic anticoagulation therapy. Hepatoxicity: vanishing bile duct syndrome[b]
	4.8	Monotherapy table, new ADRs: cutaneous vasculitis, pneumonia, embolism arterial. Combination therapy table, new ADRs: cutaneous vasculitis, vanishing bile duct syndrome, embolism arterial
Cefotaxime • DBL Cefotaxime	4.8	Kounis syndrome[c]
Dasatinib • Sprycel	4.4 4.8	Hepatoxicity
Diazoxide • DBL Diazoxide	4.8	Pericardial effusion
Dolutegravir • Tivicay • Dovato	4.6	Pregnancy: no increased risk of neural tube defects with exposure at conception
Durvalumab • Imfinzi	4.2	Treatment modifications for immune-mediated Guillain-Barré syndrome (GBS)
	4.4	Other immune-mediated adverse reactions: GBS, immune-mediated arthritis
	4.8	Uveitis, immune-mediated arthritis, GBS
Fluorouracil • Fluorouracil Accord	4.6	Pregnancy: women of childbearing age should avoid pregnancy, use highly effective contraception during pregnancy and for at least 6 months after the last dose; men should not father a child during and for at least 3 months following cessation of treatment
Finasteride • Propecia	4.8	Suicidal ideation
Glatiramer acetate • Copaxone	4.6	Lactation: updated with human data
Hydroxychloroquine • Plaquenil	4.5	Interactions with CYP inhibitors/inducers and P-gp substrates

Continues

Active ingredient(s): • Medicine(s)	Data sheet updates Section[a]	Summary of new safety information
Hyoscine • Scopoderm		Newly published data sheet
Lamivudine • Zeffix	4.4	Advice for use in patients with HIV/HBV co-infection
Lamotrigine • Lamictal	4.8	Erythema multiforme
Mercaptopurine • Puri-nethol	4.1	Removal of chronic granulocytic leukaemia
	4.4	Warnings for: hepatoxicity – cholestasis of pregnancy; NUDT15 mutation; macrophage activation syndrome; metabolism and nutrition disorders; paediatric population; galactose intolerance, complete lactase deficiency or glucose-galactose malabsorption
	4.8	Hypoglycaemia, stomatitis, cholestasis of pregnancy, bacterial and viral infections, infections associated with neutropenia, mucosal inflammation
Minocycline • Mino Tabs (Minomycin)	4.2	Administration instructions to reduce the risk of oesophageal irritation ulceration. Maximum doses for children >12 years of age
	4.4	Hyperpigmentation
	4.8	Fixed drug eruptions, enamel hypoplasia, decreased hearing, headache not related to benign intracranial hypertension
Nirmatrelvir + ritonavir[d]	4.3	Contraindications for concomitant use with eplerenone, eletriptan, naloxegol, tolvaptan, primidone
• Paxlovid	4.8	Stevens Johnson syndrome, toxic epidermal necrolysis
Nusinersen • Spinraza	4.8	Arachnoiditis
Oxcarbazepine • Trileptal	4.6	Pregnancy: EURAP registry results, potential risk of congenital malformations and neurodevelopment disorders. Lactation: infant exposure
Plerixafor • Mozobil	4.6	Pregnancy: should not be used during pregnancy; women of childbearing potential and men should use effective contraception during treatment and for one week after cessation
Rifabutin • Mycobutin	4.3	Contraindication for concomitant use with rilpivirine
	4.4	Warnings for interactions with elvitegravir, plus anti-HCV medicines such as sofosbuvir
	4.5	Interactions with atazanavir/ritonavir, darunavir/ritonavir, dolutegravir, elvitegravir/cobicistat, etravirine, sofosbuvir, bedaquilline, ethinylestradiol/norethindrone
Rifampicin + isoniazid • Rifinah	4.4	Cerebellar syndrome
	4.8	
Rosuvastatin • Crestor • Rosuvastatin Viatris	4.5	Interaction with ticagrelor
Simvastatin • Simvastatin Viatris	4.4	Myasthenia gravis, ocular myasthenia
	4.5	Interaction with ticagrelor
	4.8	Myasthenia gravis, ocular myasthenia
Ustekinumab • Stelara	4.6	Pregnancy: data for first trimester exposure does not indicate an increased risk of fetal malformations in the newborn

Continues

Active ingredient(s): • Medicine(s)	Data sheet updates Section[a]	 Summary of new safety information
Valproic acid (sodium valproate)[e] • Epilim • Epilim IV	4.4	Males of reproductive potential: increased risk of neurodevelopmental disorders (NDD) in children born to men treated with valproate in the 3 months prior to conception; risks to children fathered more than 3 months after stopping treatment are unknown; if discontinuing treatment, continue effective contraception for 3 months; inform patients to avoid donating sperm during treatment and for 3 months after stopping treatment
Varicella zoster virus (recombinant) vaccine • Shringrix	4.5	May be given concomitantly with pneumococcal conjugate vaccine (PCV) or COVID-19 mRNA vaccine

a Data sheet sections listed in the table are: 4.1: Therapeutic indications; 4.2: Dose and method of administration; 4.3: Contraindications; 4.4: Special warnings and precautions for use; 4.5: Interaction with other medicines and other forms of interaction; 4.6: Fertility, pregnancy and lactation; 4.8: Undesirable effects

b. See the September 2023 *Prescriber Update* article about vanishing bile duct syndrome

c. As a class effect of beta-lactam antibiotics. See the September 2020 *Prescriber Update* article about Kounis syndrome

d. See the Paxlovid Dear Healthcare Professional Letter (PDF, 7 pages, 630KB)

e. See the Epilim alert communication and Dear Healthcare Professional Letter (PDF, 2 pages, 179 KB)

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