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Contents

Contents

MEDSAFE
NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY
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Suicidal Ideation and Behaviour with Atomoxetine (Strattera)

Key Messages

- Patients initiated on atomoxetine should be closely monitored for the emergence of suicidal thoughts or behaviours.
- Families and caregivers of patients being treated with atomoxetine should be informed to look out for changes in behaviour, especially depression, agitation and irritability as these may indicate the emergence of suicidal thoughts and behaviours.
- Medical advice should be sought immediately if changes in behaviour are seen.
- Atomoxetine therapy may need to be discontinued if suicidal thoughts or behaviours emerge.

Atomoxetine is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children six years of age and older and adults. Suicidal ideation is a known adverse effect, that is discussed in the data sheet and was seen in children and adolescents treated with atomoxetine during clinical trials[1].

The Centre for Adverse Reactions Monitoring (CARM) has received a report of suicidal ideation in a patient taking atomoxetine. The patient experienced gradual onset of symptoms over the first six weeks of treatment, starting with tearfulness and increasing to self-harming and suicidal ideation. The patient recovered after atomoxetine was stopped.

Suicidal ideation was observed in clinical trials in children and adolescents (5/357 in the Strattera group compared to 0/851 in the placebo group). There was one report of suicidal behaviour in the Strattera group. All patients being treated with Strattera should be observed for emergence of suicidal thoughts or behaviours, especially during the initial few months of treatment or at times of dose change.

Families and caregivers of children and adolescents being treated with Strattera should be informed of the need to monitor these patients for emergence of suicidal thoughts or behaviours that may include signs of agitation, irritability or unusual changes of behaviour. If any of these symptoms develop, medical advice should be sought immediately.

References

1. Eli Lilly and Company (NZ) Limited. 2013. *Strattera Data Sheet*. 6 August 2013. URL: **www.medsafe.govt.nz/profs/Datasheet/s/Stratteracap.pdf** (accessed 1 May 2014).

Antibiotics and Tooth Staining

Key Messages

- Superficial discolouration or staining of the teeth has been rarely reported in association with some antibiotics, particularly if an oral suspension is used.
- The discolouration can usually be removed by careful brushing or professional cleaning.

Intrinsic, permanent tooth discolouration is well known to occur with the use of tetracycline antibiotics if taken during tooth development (ie, the last half of pregnancy, infancy and in childhood up to eight years of age)[1]. This is a result of tetracycline antibiotics binding to calcium and depositing in developing teeth and bones[1].

Healthcare professionals are also reminded that extrinsic or superficial discolouration of the teeth has been reported with both tetracycline and beta-lactam antibiotics. The Centre for Adverse Reactions Monitoring has received six reports of extrinsic tooth discolouration with the use of antibiotics in the past three years. Three of these reports were associated with the tetracycline class of antibiotics (doxycycline and minocycline) and three with the beta-lactam/penicillin class of antibiotics (phenoxymethylpenicillin and amoxicillin). The onset ranged from day one through to the third month of treatment.

It is thought that this discolouration may be due to formation of deposits on the tooth surface, with teeth appearing to have brown, yellow

or grey stains[2]. In most instances of extrinsic discolouration, the effect is reversible and can be removed by careful brushing or professional cleaning.

Some beta-lactam/penicillin antibiotic data sheets list superficial discolouration of the teeth as a rare adverse reaction and all tetracycline antibiotic data sheets list tooth discolouration as a general precaution. Medsafe is currently working with the sponsors to ensure data sheets are updated for all antibiotics where this is an issue.

References

1. Sanchez AR, Rogers RS, Sheridan PJ. 2004. Tetracycline and other tetracycline-derivative staining of the teeth and oral cavity. *International Journal of Dermatology* 43(10): 709-15.
2. Garcia-Lopez M, Martinez-Blanco M, Martinez-Mir I, et al. 2001. Amoxycillin-Clavulanic Acid-Related Tooth Discoloration in Children. *Pediatrics* 108(3): 819-20.

Zopiclone and Next-day Impairment

Key Messages

- ⌘ Patients taking zopiclone should be warned that their ability to drive or operate dangerous machinery may be impaired the next day.
- ⌘ Effects on driving performance may be significantly impaired for at least 11 hours after taking the medicine.
- ⌘ Zopiclone is intended for occasional use in adults at a dose of 7.5 mg orally shortly before bedtime. It should not be used for more than four weeks.
- ⌘ The initial dose should be reduced in older people.

Zopiclone is used for the treatment of short-term and chronic insomnia in adults. This includes difficulties with falling asleep (initial insomnia) and night time awakening (middle insomnia).

Patients taking zopiclone should be warned that their ability to drive or operate dangerous machinery may be impaired the next day. Importantly the patient may not be aware that they are impaired, especially if they feel they have had a good night's sleep.

A recent article concluded that zopiclone 7.5 mg caused a significant impairment of driving performance for at least 11 hours after administration. These effects did not differ between males and females and did not increase with age[1].

Concomitant intake of even small amounts of alcohol is also known to increase the risk of zopiclone adversely affecting a patient's driving ability[2].

In the last 10 years, the Centre for Adverse Reactions Monitoring (CARM) has received 15 reports of psychomotor impairment experienced within 24 hours of taking zopiclone. The reported reactions include impaired concentration, somnolence (sleepiness), headache and hangover.

In adults, the usual dose is 7.5 mg shortly before bedtime for a maximum of 2–4 weeks[2,3]. Due to poorer metabolism, the dose for older people is reduced to an initial dose of 3.75 mg.[2,3] To reduce the risk of next-day impairment, this dose of 3.75 mg should not be exceeded.

Prescribers are also reminded that zopiclone should only be used as a short term treatment (should not exceed four weeks).

References

1. Leufkens TR, Vermeeren A. 2014. Zopiclone's residual effects on actual driving performance in a standardized test: a pooled analysis of age and sex effects in 4 placebo-controlled studies. Clinical Therapeutics 36(1): 141-150.
2. Sanofi-Aventis New Zealand Limited. 2011. *Imovane Data Sheet*. 31 May 2011. URL: **www.medsafe.govt.nz/profs/datasheet/i/Imovanetab.pdf** (accessed 24 April 2014).
3. Apotex NZ Ltd. 2011. *Apo-Zopiclone Data Sheet*. 13 May 2011. URL: **www.medsafe.govt.nz/profs/datasheet/a/Apozopiclonetab.pdf** (accessed 24 April 2014).

Paracetamol and Serious Skin Reactions

Key Messages

- ⌘ Paracetamol is associated with a risk of serious skin reactions.
- ⌘ Patients should be advised to seek medical advice immediately if signs or symptoms of serious skin reactions occur.
- ⌘ Paracetamol should be discontinued in the event of a serious skin reaction.

Paracetamol is widely used to reduce pain and fever and can be purchased over-the-counter in addition to being prescribed. Paracetamol is available as a single-ingredient product and in combination products, including cough and cold preparations.

The US Food and Drug Administration (FDA) recently issued a drug safety communication warning that paracetamol can, in rare cases, cause serious skin reactions, also known as Severe Cutaneous Adverse Reactions (SCARs)[1].

SCARs include Stevens Johnson Syndrome, toxic epidermal necrolysis, acute generalised exanthematous pustulosis, and erythema multiforme. These reactions can occur when using paracetamol for the first time or at any time during administration, and can be fatal. It is likely that these reactions occur rarely.

The Centre for Adverse Reactions Monitoring (CARM) has received four reports of serious skin reactions causally associated with paracetamol. These included two reports of erythema multiforme, one of toxic epidermal necrolysis and one of Stevens Johnson Syndrome.

Patients should be advised to consult their doctor at the first appearance of a skin rash, skin peeling, mouth ulcers, or any sign of hypersensitivity. If serious skin reactions occur, discontinue paracetamol immediately.

Non-steroidal anti-inflammatory drugs (NSAIDs) also used to treat fever and pain/body aches, can also cause SCARs[2]. However, there does not appear to be cross-sensitivity between paracetamol and other medicines that reduce pain and fever[1].

References

1. Food and Drug Administration, 2013. FDA warns of rare but serious skin reactions with the pain reliever/fever reducer acetaminophen. *FDA Drug Safety Communication* 1 August 2013. URL: **www.fda.gov/drugs/drugsafety/ucm363041.htm** (accessed 24 April 2014).
2. Medsafe. 2012. NSAIDs can SCAR (Severe Cutaneous Adverse Reaction). *Prescriber Update* 33(2): 11–12. URL: **www.medsafe.govt.nz/profs/PUArticles/NSAIDScanSCARJune2012.htm** (accessed 24 April 2014).

Reminder: Olanzapine Depot and Post-injection Syndrome

Key messages

- ⌘ Olanzapine pamoate depot injection carries a small risk of post-injection syndrome.
- ⌘ Patients must to be monitored for at least two hours after each dose.
- ⌘ Symptoms of post-injection syndrome include sedation, confusion, agitation, anxiety, aggressiveness, dizziness, ataxia and extrapyramidal symptoms.
- ⌘ In most cases, symptoms appear within one hour following injection and resolve within 24–72 hours.
- ⌘ Healthcare professionals are advised to discuss this potential risk with patients each time they prescribe and administer olanzapine pamoate depot injection.

Healthcare professionals are reminded that patients who receive olanzapine pamoate depot injection must be monitored for at least two hours after each dose[1].

Olanzapine pamoate is an antipsychotic depot formulation for injection, designed to release olanzapine slowly from the intramuscular site. It is administered by deep intramuscular injection into the gluteal region every two to four weeks.

Post-injection syndrome has been estimated to occur after 0.07% of olanzapine depot injections and in approximately 1.4% of treated patients[2]. The syndrome is yet to be convincingly linked to depot antipsychotics other than olanzapine. Post-injection syndrome includes a range of signs and symptoms such as sedation and delirium that are consistent with olanzapine overdose. Other symptoms include dizziness,

weakness, aggression, ataxia hypertension and seizures. Extrapyramidal symptoms are also reported, such as tremor, dystonia, akathisia, and tardive dyskinesia.

Initial signs and symptoms of post-injection syndrome appear within one hour following injection[1]. In most cases full recovery is expected to occur within 24–72 hours after injection. There is no specific reversal agent for olanzapine depot injection and treatment of post-injection syndrome is management of the symptoms.

The Centre for Adverse Reactions Monitoring (CARM) has received 14 reports of reactions following olanzapine pamoate injection that suggested a post-injection syndrome had occurred. Patients experienced reactions including sedation, ataxia, slurred speech, blurred vision, confusion, agitation, and extrapyramidal symptoms. The time to onset of symptoms ranged from 'immediate' to one hour following injection. The dose and interval between doses varied considerably. Most patients required overnight observation in hospital.

Cases of post-injection syndrome have also been reported internationally. The FDA issued an alert in June 2013 over three unexplained deaths in patients who had received olanzapine depot injection. The following link provides more details: **www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm357601.htm**

Healthcare professionals are advised to discuss the potential risk of post-injection syndrome with their patients prior to administering each dose of olanzapine pamoate.

Please report any adverse reactions to the CARM. The following link provides more information about how to report: **www.medsafe.govt.nz/safety/report-a-problem.asp**

References

1 Eli Lilly and Company (NZ) Limited. 2013. *Zyprexa Relprevv Data Sheet* 31 January 2013. URL: **www.medsafe.govt.nz/profs/datasheet/z/zyprexarelprevvinj.pdf** (accessed 12 May 2014).

2. Novakovic V, Adel T, Peselow E et al. 2013. Long-acting injectable antipsychotics and the development of postinjection delirium/sedation syndrome (PDSS). *Clinical Neuropharmacology* 36:59–62.

St John's Wort and Implanted Hormonal Contraceptives

St John's wort (*Hypericum perforatum*) is a herbal medicine traditionally used to relieve low mood. The interaction between St John's wort and contraceptives was highlighted by Medsafe in 2000[1].

In addition to potentially interacting with oral hormonal contraceptives, St John's wort has now been noted to interact with implanted hormonal contraceptives.

There have been overseas reports of unplanned pregnancies associated with use of St John's wort in women who have implanted hormonal contraceptives. Prescribers should advise women using any hormonal contraceptives for pregnancy prevention to avoid herbal products containing St John's wort or to use an additional form of contraception when they are using such products[2,3].

In New Zealand although there have not been any reports of pregnancy in women using hormonal contraceptives and St John's wort concomitantly, there have been three reports of breakthrough bleeding.

Prescribers are encouraged to report suspected adverse events related to complementary medicines to CARM. Doctors are encouraged to ask patients explicitly about complementary medicine use, as such use may not be volunteered when patients are asked about the medications they are using.

References

1. Medsafe. 2001. Interactions with St John's wort (Hypericum perforatum) preparations. *Prescriber Update*, 20: 42-48.

2. MHRA. St John's wort: interaction with hormonal contraceptives, including implants – reduced contraceptive effect. *Drug Safety Update* 7: A2, No. 8, 13 Mar 2014. Available from: URL: **www.mhra.gov.uk/home/groups/dsu/documents/publication/con392897.pdf**

3. Stockley IH. 2002. *Stockley's Drug Interactions*. London: Pharmaceutical Press.

Risk of Fibrosis with Medicines Containing Ergot Derivatives

Key Messages

- Long-term use of medicines containing ergot derivatives (bromocriptine, cabergoline and ergotamine) has been associated with fibrosis.
- Patients who need to take these medicines long-term should be monitored for the signs and symptoms of fibrosis. Treatment should be discontinued if fibrosis is diagnosed.

Ergotamine and ergot derivatives are associated with an increased risk of fibrosis, the formation of excess connective tissue. Ergot derivatives are recognised as being capable of inducing fibrosis, particularly of the heart valves, through serotonergic receptor activation. Fibrosis is often difficult to diagnose because of delayed symptoms and may be irreversible.

Medicines containing ergotamine derivatives include: bromocriptine, cabergoline (Dostinex) and ergotamine (Cafergot).

The risk of fibrosis is greater when these medicines are used for long-term treatment such as in Parkinsons Disease (bromocriptine) and chronic endocrine disorders (bromocriptine and cabergoline). The risk of cardiac fibrosis is greatest with cabergoline and pergolide (pergolide is no longer available in New Zealand).

Since the risk of fibrosis may be related to length of use it is not thought to apply to short-term uses such as suppression of lactation or occasional use for treatment of migraine (Cafergot). However, use of Cafergot that exceeds the maximum recommended dose of 10 tablets per week, may still induce fibrotic changes. Cafergot should not be used in children under 12 years of age.

All patients who need to take ergotamine derived medicines long-term should be monitored for possible manifestations of fibrosis. Signs and symptoms include dyspnoea, persistent cough, chest pain, heart failure, renal insufficiency or urethral/abdominal obstruction.

References

1. Pfizer New Zealand Ltd. 2013. *Dostinex Data Sheet*. 20 March 2013. URL: **www.medsafe.govt.nz/profs/Data sheet/d/Dostinextab.pdf** (accessed 1 May 2014).
2. Apotex NZ Ltd. 2014. *Apo-bromocriptine Data Sheet*. 28 April 2014. URL: **www.medsafe.govt.nz/profs/Data sheet/a/Apobromocriptinetab.pdf** (accessed 1 May 2014).
3. AFT Pharmaceuticals Ltd. 2014. *Cafergot Data Sheet*. February 2014. URL: **www.medsafe.govt.nz/profs/Data sheet/c/cafergottab.pdf** (accessed 1 May 2014).

Quarterly Summary of Medsafe's Early Warning System Communications

More information about the early warning system can be found on the Medsafe website (**www.medsafe.govt.nz/Projects/B2/EWS.asp**).

16 May 2014	Alert	Cook Petite Vital Port, adherence of tubing to the vessel wall leading to complications in explanting the device
5 May 2014	Alert	Provive MCT – LCT 1% Emulsion for Injection (10mg/mL) and Provive 1% Emulsion for Injection (10mg/mL) – investigation of infection in Australia
9 April 2014	Monitoring	Allopurinol and lichenoid-type skin reactions added to the medicines monitoring scheme
1 April 2014	Monitoring	Doxazosin and a possible risk of nightmare (paroniria) added to the medicines monitoring scheme
31 March 2014	Alert	Domperidone (Motilium, Prokinex) and effects on the heart

If you would like to receive Medsafe's early warning communications you can subscribe at **www.medsafe.govt.nz/profs/subscribe.asp**

Terazosin and Hypotension

Key Messages

- Terazosin can cause marked hypotension and syncope when taking the first dose or first few doses.
- The recommended starting dose is 1 mg taken at bedtime to minimise the risk of a hypotensive event.

Terazosin is well documented to cause marked lowering of blood pressure, especially postural hypotension, and syncope in association with the first dose or first few doses[1]. These effects can also occur if terazosin is interrupted for more than a few doses then restarted.

The Centre for Adverse Reactions Monitoring (CARM) recently received a report of an elderly patient who collapsed and became unresponsive after taking their first dose of terazosin. The patient recovered after first aid treatment. CARM has received two further reports of patients suffering severe hypotension or cardiac arrest after taking a first dose of terazosin.

Terazosin is indicated for treatment of benign prostatic hyperplasia (BPH) and is also indicated in the treatment of hypertension.

To minimise the risk of hypotensive events, the recommended starting dose for patients is 1 mg to be taken at bedtime. If this dose is tolerated, then the dose can be slowly increased.

Patients who have had a hypotensive adverse event following the first dose should avoid terazosin. Other treatment options should be considered.

Further information on dosing and adverse effects can be found in the data sheets on the Medsafe website (**www.medsafe.govt.nz/profs/Datasheet/dsform.asp**).

References

1. Abbott Laboratories (NZ) Ltd. 2010. *Hytrin Data Sheet*. April 2010. URL: **www.medsafe.govt.nz/profs/datasheet/h/Hytrintab.pdf** (accessed 1 May 2014).

MARC's Remarks: March 2014 Meeting

The Medicines Adverse Reactions Committee (MARC) met on 13 March 2014 to review a number of medicine related safety issues.

The MARC discussed the need for additional safety monitoring for **rotavirus vaccine** (RotaTeq) once it is included on the National Immunisation Schedule from 1 July 2014. The MARC considered Medsafe's proposed monitoring actions, which include periodic CARM reports and routine assessment of PSURs, to be appropriate. This vaccine has been used widely and successfully for several years in other countries.

The MARC reviewed information on a possible interaction between **varenicline** and alcohol that had been placed on the M² scheme. The MARC noted that data available on this potential interaction are limited both in quality and quantity. However, the MARC recommended that information on this potential interaction should be strengthened in the Champix data sheet.

Further information on these issues can be found on the Medsafe website (**www.medsafe.govt.nz/profs/adverse/Minutes157.htm**).

WE NEED YOUR HELP!

Please send your reports for these potential safety issues listed in the table below.

M² MEDICINES MONITORING

Medicine	Potential safety issue	Active monitoring ends
Allopurinol	Lichenoid-type skin reactions	31 October 2014
Doxazosin	Nightmare	31 October 2014
Amitriptyline	Peripheral coldness/Raynaud's phenomenon	31 July 2014

Correction: Adverse Reaction Reporting in New Zealand – 2013

The March 2014 edition of *Prescriber Update* included an article about adverse reaction reporting in New Zealand in 2013[1]. The numbers of adverse reaction reports included in the article were incorrect. The online article on the Medsafe website has been updated with the correct numbers.

The total number of suspected adverse reaction reports received by the Centre Adverse Reactions Monitoring (CARM) in 2013 was 4138. The percentages of medicines, vaccines, and complementary and alternative medicines (CAMs) were 64.2%, 35.6% and 0.2% respectively. For CAMs, 29% of reports described reactions that were considered as serious.

References

1. Medsafe. 2014. Adverse Reaction Reporting in New Zealand – 2013. *Prescriber Update* 35(1): 7–8. URL: **www.medsafe.govt.nz/profs/PUArticles/March 2014 Adverse ReactionReporting2013.htm** (accessed 20 March 2014).

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