

Prescriber Update

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Adulterated erectile dysfunction products: on the rise in New Zealand

Products marketed in New Zealand as 'herbal' supplements for erectile dysfunction and sexual performance are increasingly being found to contain undeclared prescription medicines.

Since July 2009 Medsafe has identified 29 products that claim to be naturally derived to enhance sexual performance that have been adulterated with prescription medicines such as the PDE5 inhibitors: sildenafil, tadalafil, and vardenafil. In some cases products have been adulterated with a combination of PDE5 inhibitors.

Adulterated erectile dysfunction products have been found being sold in pharmacies, sex shops, herbal remedy stores and through New Zealand based internet sites. Brand names include *So Hard for Men*, *Pulse8 for Women*, *The Rock*, *Stallion*, and *Volcanic*.

Doses contained in these products vary considerably and are commonly either within the therapeutic range or above recommended doses. A product identified as adulterated was recently found to contain 25mg of tadalafil with additional tadalafil and sildenafil within the gelatine capsule shell. The maximum recommended dose of tadalafil (Cialis®) is 20mg per day.

Although erectile dysfunction supplements are the most commonly identified as being adulterated, supplements for weight loss have also been found to contain sibutramine and phenolphthalein.

Healthcare professionals are advised to warn their patients about the dangers of using these supplements due to the risk that they may contain undeclared ingredients. It is also worth considering that your patient may be taking an adulterated product if they are experiencing unexplained symptoms or adverse reactions.

Please contact the Medsafe Compliance Management Team on Ph: (04) 819 6800 if you are suspicious that a product may have been adulterated.

Renal dangers associated with long term lithium use

Prescribers are reminded that long-term lithium therapy can cause renal failure along with other

metabolic adverse effects including hypothyroidism, weight gain, and hyperparathyroidism. Renal function, including glomerular filtration rate (GFR) should be measured regularly even after 10 – 15 years of therapy. If renal impairment develops, advice from a nephrologist and/or psychiatrist should be sought as discontinuing lithium therapy may not be possible for all patients.

Lithium is associated with a number of renal adverse effects including nephrogenic diabetes insipidus (which affects up to 40% of patients), chronic kidney disease (CKD) and renal failure.¹

The Centre for Adverse Reactions Monitoring (CARM) has received a total of nine reports of renal failure in association with lithium use. Importantly, six of the reports were received in the last two years. The mean age of patients was 53 years (range 36-77 years) and the average duration of lithium therapy prior to development of CRF was 28 years (range 14-38 years). In at least one case, renal function continued to deteriorate despite lithium being discontinued.

The CARM reports are consistent with published literature^{1,2} in that renal failure developed slowly over several decades and discontinuation of lithium did not significantly reduce the rate of progression of disease in all cases. Possible risk factors identified include: increasing age; episodes of lithium toxicity; and other risk factors for CKD including diabetes, hypertension and concurrent use of long-term non-steroidal anti-inflammatory drugs.^{1,3}

These cases highlight the need for continued monitoring of renal function to ensure early detection and management of renal impairment, although progression to renal failure may not be avoidable. Management options include the use of an alternative agent; however the psychiatric consequences of such action need to be carefully considered. Further information and advice has been published by BPAC in New Zealand and NICE in the United Kingdom, including a detailed list of monitoring requirements.^{3,4}

Please report all serious reactions to medicines to CARM even if they are known. These reports can provide useful information on new risk factors or interactions with other medicines or foods.

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4. National Institute for Health and Clinical Excellence (2006). The management of bipolar disorder in adults, children and adolescents, in primary and secondary care. (Clinical guideline 38, section 1.6.2.10) www.nice.org.uk/Guidance/CG38

Fentanyl patches – different brands are not interchangeable

Prescribers are advised that a new brand of fentanyl patch has been approved. However, patients should not be changed from one brand of fentanyl patch to another. If for any reason the brand needs to be changed the dose should be re-titrated and the patient's response clinically assessed.

Fentanyl, a potent opioid analgesic, is only recommended for patients who have opioid tolerance due to the risk of developing respiratory depression.

Experience in other countries has shown that patients and caregivers need support and counselling to ensure they are fully informed of the correct use of these patches. Patients and caregivers must be advised to:^{1,2}

- Follow the prescribed dose.
- Apply and remove the patch at the correct frequency.
- Ensure old patches are removed before applying the new one.
- Not cut the patch.
- Avoid touching the adhesive side of patches.
- Wash hands after application.
- Keep out of reach and sight of children.

Patients wearing fentanyl patches who experience an increase in body temperature or expose the patches to external heat may develop clinically significant increases in fentanyl blood levels. Therefore patients should not use heat sources such as heating pads, electric blankets, heat or tanning

lamps, hot water bottles, prolonged hot baths, saunas or hot whirlpool spa baths while wearing fentanyl patches.

Patients and caregivers need to be aware of the signs and symptoms of fentanyl overdose. Patients experiencing any of the following should seek immediate medical attention:

- Trouble breathing or slow or shallow breathing.
- Slow heartbeat.
- Severe sleepiness.
- Cold, clammy skin.
- Trouble walking or talking.
- Feeling faint, dizzy or confused.

If serious adverse reactions to the patch do occur it should be removed immediately and the patient should be monitored for up to 24 hours.

Further information on the use of fentanyl patches can be found in the product data sheets on the Medsafe website: www.medsafe.govt.nz/profs/Datasheet/dsform.asp

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Transdermal medicine patches – risk of burns during MRI scans

Healthcare professionals are advised that transdermal patches containing metal can overheat during MRI scans and have been reported to cause discomfort or skin burns in the immediate area of the patch.

When referring patients for MRI scans, healthcare professionals should advise patients to inform the technologist if they are wearing a transdermal patch. Unless the technologist advises otherwise the patch should be removed and disposed of before the scan, then replaced after the scan.

Many transdermal patches, such as nicotine replacement or pain relieving patches, are also available without a prescription meaning Medical Radiation Technologists should check if patients are using transdermal patches before MRI scans.

Some patches contain metal in the backing of the patch, which is not always visible.

The use of varenicline (Champix) in NZ: key findings from IMMP study

Dr Mira Harrison-Woolrych, Head, IMMP

Prescribers are reminded that the varenicline product information advises a 12 week course of treatment commencing with a starter pack and that failure to complete the course may have implications for the effectiveness of this smoking cessation treatment.¹

A recently published study from the NZ Intensive Medicines Monitoring Programme (IMMP) on the use of varenicline (Champix) had the following key findings:²

- The majority of patients did not receive 12 continuous weeks of varenicline treatment as recommended in the Champix product information.
- The most commonly reported reasons for not completing the 12 week course were adverse reactions and the cost of treatment.
- Doctors prescribing varenicline appeared to believe patients were completing the 12 week course when IMMP dispensing records showed that most did not.
- The effectiveness of varenicline in a sub-group of this cohort was 28% and is similar to that reported in clinical trials.

References

1. Pfizer Ltd. New Zealand datasheet for Champix. 2009. Available at: <http://www.medsafe.govt.nz/profs/Datasheet/dsform.asp>
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Reminder – skin cancer risk with immunosuppressant treatment

Immunosuppressant treatment is associated with an increased risk of cancer.

In New Zealand patients the high levels of UV radiation means the risk of skin cancer is a particular concern. It is now thought that immunosuppressed patients may be at even higher risk of skin cancer if they also experience photosensitivity reactions caused by concomitant medicines such as voriconazole or co-trimoxazole for example.¹

With summer approaching prescribers are asked to remind patients about the risk of skin cancer and how to perform self skin examination. Guidance is published on the New Zealand Dermatological Society website: <http://www.dermnetnz.org/procedures/self-skin-examination.html>

Further information on photosensitivity reactions in New Zealand was published in the February 2010 edition of *Prescriber Update*: <http://www.medsafe.govt.nz/profs/PUArticles/Summerreminder-photosensitivityreactions.htm>

References

1. Miller DD, Cowen EW, Nguyen JC et al 2010 Melanoma associated with long-term voriconazole therapy: a new manifestation of chronic photosensitivity. *Arch Dermatol* 146 (3) 300-4.

Complementary corner: Propolis – reports of hypersensitivity reactions

Healthcare professionals are advised to consider the uncertain benefits of propolis versus the risk of developing hypersensitivity reactions or renal failure before recommending its use to patients.

This advice follows a review of international adverse reaction reports that identified several cases of hypersensitivity reactions in people using complementary medicines containing propolis.¹ Patients with a history of allergies appeared to be at particular risk of these reactions. Propolis has also been implicated in cases of acute renal failure.^{2,3}

Propolis is a resinous mixture collected by honey bees from tree buds, sap and other botanical sources. It is marketed as a traditional medicine for

the relief of a wide variety of conditions, including inflammation, viral diseases, ulcers, superficial burns and scalds; however none of these claims have been confirmed by clinical studies published in the biomedical literature.⁴

The composition of propolis depends, among other factors, on geographical location and season; a 'typical' propolis may contain around 50 constituents including resins, vegetable balsams, waxes, essential oils and pollen.

Healthcare professionals are also reminded to ask patients about their use of OTC and complementary medicines, and to report any adverse reactions to CARM.

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Ketamine classification change – important information

Healthcare professionals are advised that ketamine will become a Class C(4) controlled drug on **1 December 2010**. After this date ketamine will need to be stored in a safe and will be added to the list of drugs that have to be prescribed on a triplicate controlled drug prescription.

Ketamine labels will be updated to identify this substance as a C4 controlled drug and an importation licence will be required for each consignment that is to enter New Zealand. Advertising ketamine will also be prohibited except where intended for medical practitioners, dentists, veterinarians and pharmacists.

The classification change is designed to reduce the potential for diverting ketamine for non-legitimate purposes and is similar to controls introduced in other countries.

Beware of systemic fungal infections in patients taking monoclonal antibodies

Monoclonal antibodies (Mabs), designed to suppress part of the immune system, can cause profound immunosuppression in some patients.

These patients are at risk of developing invasive fungal infections such as histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis and pneumocystosis. These infections can go unrecognised unless a high index of suspicion is maintained. Delays in treatment can result in serious adverse outcomes.

Healthcare professionals are reminded to monitor patients closely during and after treatment for the development of signs and symptoms of systemic fungal infection. Symptoms include fever, malaise, weight loss, sweats, cough, dyspnoea, pulmonary infiltrates on x-ray or serious systemic illness.

Patients who develop a systemic fungal infection should have their Mab therapy reviewed and be appropriately treated. If Mab therapy is discontinued it can be restarted on recovery; however a re-evaluation of the benefits and risks of treatment should be discussed with the patient.

Further information on systemic fungal infections can be found at: <http://dermnetnz.org/fungal/systemic-mycoses.html>

Further information on individual medicines can be found on the Medsafe website: <http://www.medsafe.govt.nz/profs/Datasheet/dsform.asp>

Healthcare professionals are reminded to continue to report any suspected adverse reactions associated with these medicines to CARM.

The use of antidepressants in pregnancy

In 2008 Medsafe provided advice on the use of Selective Serotonin Reuptake Inhibitors (SSRIs) in pregnancy.¹

Since that time further epidemiological studies have been published.²⁻⁵ The Medicines Adverse Reactions Committee (MARC) has reviewed these studies investigating the association between SSRI or serotonin noradrenaline reuptake inhibitor (SNRI) treatment and congenital anomalies. The

MARC concluded that there is a small increased risk of congenital cardiac defects associated with fluoxetine, similar to that seen with paroxetine.⁶ The possibility of a class effect for all SSRIs or a similar effect with SNRIs could not be excluded.

In addition to the risk of congenital anomalies SSRIs and SNRIs have been associated with an increase in risk of pre-term birth, persistent pulmonary hypertension of the newborn (PPHN) and neonatal withdrawal symptoms when the mother is treated until the birth of the baby.

There is less information on the use of tricyclic antidepressants (TCA) in pregnancy. However, a recent epidemiological study indicated that TCAs may also be associated with an increased risk of congenital anomalies, pre-term birth and neonatal withdrawal symptoms.⁷

It is important to remember that untreated antenatal depression has also been associated with adverse outcomes for both mother and foetus. The decision to treat a pregnant woman with antidepressant medicines can only be made on an individual basis in collaboration with the patient. The risks associated with ineffective treatment need to be balanced with the small increase in risk of congenital abnormalities, pre-term birth and neonatal withdrawal symptoms.

Healthcare professionals should be aware of the use of antidepressants in pregnancy and should closely observe neonates exposed to antidepressants for signs of withdrawal symptoms or PPHN.

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Graseby pump withdrawal – change to target date and alternative

Healthcare professionals are advised that Medsafe has extended its target date for the withdrawal of Graseby MS-Series syringe drivers from clinical use to **30 June 2011**. This change is due to further problems being experienced with the supply of alternative syringe drivers.

CareFusion, the supplier of the alternative AD syringe driver, has advised that it is no longer able to guarantee timelines and support for the AD syringe driver and cannot continue its supply.

A transition team has been established to provide advice on alternative options; however a recommendation on the alternative supplier is yet to be finalised. The transition team includes clinical, operational, biomedical engineering, procurement and Medsafe representatives.

In the meantime, please note the following key points:

- The AD syringe drivers can continue to be safely used until transitioned to an alternative device.
- No new AD syringe drivers will be supplied in New Zealand via CareFusion.
- All Graseby syringe drivers must be removed from clinical use by 30 June 2011.
- A transition plan will be circulated once an alternative device has been confirmed.
- Appropriate clinical and technical training will be provided for the new device prior to any transition.
- Current AD syringe driver customers will be contacted in the coming weeks to assist with transition planning.

Medsafe continues to closely monitor this process and will ensure regular updates are provided to healthcare professionals during the transition process.

Safety concerns over the use of Graseby MS-Series Syringe Drivers were first raised by Medsafe in 2007 and prompted the manufacturer, Smiths Medical, to discontinue further supply later that year.

Apotex metformin tablets cannot be accurately halved

Healthcare professionals are advised that the Apotex brand of metformin 500mg and 850mg tablets are not scored and cannot be accurately halved. This advice follows recent reports sent to CARM describing problems halving the 500mg tablet.

The recommended starting dose for metformin is 500mg once or twice daily; however Medsafe is aware that some patients are being prescribed a starting dose of 250mg to minimise gastrointestinal side effects. Diarrhoea, nausea and vomiting occur in more than 10% of patients starting metformin but usually resolve over a short period of time.

Medsafe has obtained expert advice on metformin dosing and has been informed that a 250mg daily dose is likely to be subtherapeutic. This means any small differences in dose resulting from inaccurate halving of a 500mg tablet are unlikely to be clinically relevant. Similarly, any small differences from inaccurate halving are unlikely to affect the development of gastrointestinal tolerance.

Prescribers are also advised to consider the difficulties associated with halving a 500mg tablet and remember that an 850mg tablet is available before titrating metformin doses in increments of 250mg.

Further information on metformin dosing can be found on the Medsafe website at: <http://www.medsafe.govt.nz/profs/Datasheet/dsform.asp>

Rosiglitazone and cardiovascular risk – current advice

Following international scrutiny of the risk of cardiovascular events in patients treated with rosiglitazone, prescribers are advised to carefully follow the contraindications, warnings, precautions and monitoring requirements for this medicine.¹⁻³

Prescribers are reminded that rosiglitazone is not recommended for:

- Patients with symptomatic heart failure.
- Patients with acute coronary syndrome or ischaemic heart disease.
- Patients who are already receiving insulin.

Patients who are treated with rosiglitazone need to be monitored for signs and symptoms of adverse reactions relating to fluid retention, including weight gain and heart failure. Rosiglitazone should be discontinued if any deterioration in cardiac status occurs.

Medsafe and the Medicines Adverse Reactions Committee continue to monitor the safety of rosiglitazone. Further information on the use of rosiglitazone is available at: <http://www.medsafe.govt.nz/profs/Datasheet/dsform.asp>

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