

Prescriber Update

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FROM THE EDITOR

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Immunisation Handbook 2006

The *Immunisation Handbook 2006* (Handbook) is now available as a PDF document for download from the Ministry of Health web site (www.moh.govt.nz/immunisation). Printed copies of the Handbook will be mailed to the immunisation sector when available, and can also be ordered from the web site. The Handbook provides information for health professionals on vaccine-preventable diseases, the vaccines available, and the updated National Immunisation Schedule, as well as practical advice and strategies for health professionals immunising children and adults in New Zealand.

MeNZB adverse events

Safety monitoring reports summarising the types and numbers of adverse events reported following vaccination with MeNZB are available on the Ministry of Health's web site: www.immunise.moh.govt.nz/safety/safetymonitoringreports.html

Travel medicine information 2005 edition: www.who.int/ith

International Travel and Health is a World Health Organisation publication about the health risks likely to be encountered in specific countries and associated with different types of travel. This guide provides medical professionals with information about potential risks as well as providing advice regarding recommended vaccinations, protection against insects and other disease vectors, and safety in different environmental settings. The most recent (2005) edition can be viewed on-line (for no charge) at www.who.int/ith. Hard-copies can also be purchased through this same web site.

Key to *Prescriber Update* articles

To assist readers in knowing the origin of articles published by Medsafe, the symbols below will appear next to the article title, where applicable.



Adverse Drug Reaction Update articles are written in response to adverse reaction reports lodged with the Centre for Adverse Reactions Monitoring (CARM) and material in the international literature. These articles may also be written to alert prescribers and pharmacists to potential problems with medicines.



MARC Prescribing Advice articles are recommendations from the Medicines Adverse Reactions Committee (MARC) in response to medicine safety issues and overseas experiences.

WATCHING BRIEFS

Quick updates, alerts and short reminders about medicine safety issues

SSRI-TCA interactions and serotonin syndrome

Prescribers are reminded of the potential for interactions to occur when a selective serotonin reuptake inhibitor (SSRI) antidepressant is co-prescribed with a tricyclic antidepressant (TCA). Concurrent use of SSRIs can elevate TCA plasma levels 2-4 fold, with resultant toxicity. Reported symptoms include constipation, urinary hesitancy, seizures and delirium.¹ Serotonin syndrome is another potential consequence of concurrent therapy. While TCAs and SSRIs can separately cause serotonin syndrome due to their serotonergic properties, this risk is increased when they are used together. Serotonin syndrome is a dose-dependent toxic state caused by excess serotonin within the CNS and is characterised by mental, autonomic and neuromuscular changes. Clinical features include confusion, agitation, hyperactivity, sweating, tachycardia, ataxia, hypertonia and tremor. Prompt withdrawal of the suspect medicines and supportive care are key to the treatment of serotonin syndrome.²

The long half-life of fluoxetine in particular (7-15 days) means that the potential for interactions can persist for days or weeks after withdrawal of this antidepressant. The mechanism for the increased TCA plasma levels involves SSRI inhibition of cytochrome P450 isoenzyme CYP2D6, which results in decreased TCA metabolism with resultant TCA accumulation. Should the decision be made to concurrently prescribe a SSRI and TCA, it is recommended that the dose of TCA be decreased and that the patient be closely monitored for signs of TCA toxicity and serotonin syndrome.¹ Patients should also be informed about these possible drug interactions and the warning symptoms to look out for.

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Colchicine – safe use is critical

Colchicine in overdose is extremely toxic and has resulted in fatalities. Prescribers are reminded that colchicine is now indicated as second-line therapy in the treatment of acute gout, after nonsteroidal anti-inflammatory drugs. Corticosteroids are recommended where both are contraindicated.¹

Due to the risk of dose-related serious adverse effects, the use of high doses of colchicine to treat acute gout is no longer appropriate, especially in elderly patients, patients with impaired hepatic or renal function, and patients who weigh less than 50kg. The dosing interval for colchicine has been increased from 2-3 hourly to six hourly. For otherwise healthy adults the maximum dose of colchicine in the first 24 hours is 2.5mg and the total dose given in an acute attack should not exceed 6mg over four days. Furthermore, it is no longer considered safe or appropriate to continue dosing until gastrointestinal adverse effects occur.¹

Prescribers should be aware that patients might still have supplies of colchicine at home with previous dosage advice, including instructions to continue dosing until diarrhoea occurs. Prescribers need to inform patients of the revised dosage advice for colchicine, and stress the importance of not exceeding the lowered maximum doses. Clear dosage advice (including the maximum daily and cumulative doses) should be written on the prescription so that this information can be included on the pharmacy label that is read by the patient. Patients should be warned of the symptoms of colchicine toxicity and advised to immediately discontinue therapy and see their doctor if symptoms occur.

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Nitrofurantoin – monitor lung function in long-term use

An earlier *Prescriber Update* article reported a case of fatal interstitial lung disease resulting from long-term nitrofurantoin therapy.¹ CARM continues to receive reports of acute and chronic pulmonary adverse reactions associated with nitrofurantoin. Acute pulmonary reactions typically have hypersensitivity-type features and occur 1-2 weeks after initiation of nitrofurantoin. Chronic pulmonary reactions mainly involve older persons, are often insidious in onset and associated with therapy of six months or longer. Interstitial lung disease and pulmonary fibrosis may develop so it is important to avoid any delay in the recognition of nitrofurantoin-induced lung changes.

The pulmonary function of patients undergoing prolonged nitrofurantoin therapy should be monitored. This involves careful vigilance for early features of emerging pulmonary toxicity, which may be evidenced by cough or shortness of breath, indicating the need for prompt withdrawal and further investigation including chest x-ray and spirometry. Patients should be informed of the warning symptoms and encouraged to report these early. Patients who have experienced pulmonary toxicity with nitrofurantoin should not be re-exposed.

Reference

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Proton pump inhibitors and interstitial nephritis

Acute renal impairment caused by interstitial nephritis is a recognised complication of treatment with omeprazole. Presenting symptoms may be non-specific and include malaise, fever, nausea, lethargy, weight loss, rash and eosinophilia. Patients known to be taking omeprazole who exhibit these symptoms should undergo urine microscopy and assessment of renal function. If either or both are abnormal, omeprazole should be withdrawn pending nephrology assessment.¹ Interstitial nephritis should also be considered if there is an unexpected rise in serum creatinine.

Since publishing information about omeprazole-induced interstitial nephritis in 2000,¹ there have been 21 further cases reported to CARM; nine were reported in 2005 alone. Interstitial nephritis has also been reported with pantoprazole² and lansoprazole³; CARM has received three such reports for pantoprazole. This reaction is thought to be rare but proton pump inhibitors are now believed to be the commonest cause of interstitial nephritis in the Auckland region, perhaps due to their widespread use.⁴ This suggests that prescribers should be vigilant for this adverse reaction when using omeprazole or other proton pump inhibitors.

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ALENDRONATE AND INFLAMMATORY ADVERSE REACTIONS



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Alendronate is a potent inhibitor of bone resorption and is most commonly used in the treatment and prevention of osteoporosis. Inflammatory eye disorders are now recognised adverse effects. Patients with eye pain or visual loss should be referred to an ophthalmologist. Reports to CARM indicate that alendronate may cause synovitis, which can be severe. The risk of oesophagitis and oesophageal ulceration, which may lead to stricture or perforation, should be minimised by following advice regarding posture and adequate water intake with each dose. Patients should report difficulty or pain when swallowing, retrosternal pain, and new or worsening dyspepsia.

Alendronate is indicated for osteoporosis and Paget's disease

Alendronate, a bisphosphonate, is a potent inhibitor of osteoclast-mediated bone resorption. It is indicated in postmenopausal women for the prevention and treatment of osteoporosis to prevent fractures; for the treatment of osteoporosis in men; for the treatment and prevention of glucocorticoid-induced osteoporosis; and for treatment of Paget's disease of bone. It is given orally, usually once weekly.¹ For alendronate, gastrointestinal, musculoskeletal and neurological reports comprise almost 50% of suspected adverse reactions reported to the Centre for Adverse Reactions Monitoring (CARM), and ocular reactions comprise about 4%.

Refer if ocular pain or visual loss occurs

Rare but serious ocular complications can occur with alendronate treatment. Of these, most of the clinically significant reactions reported to CARM and internationally are ocular inflammation such as conjunctivitis, uveitis, episcleritis and scleritis.^{2,3} Time to onset varied from two days to three years (median of three weeks) after commencement of treatment.³ Symptoms include abnormal or blurred vision, redness, ocular pain and photophobia.² Patients with visual loss or ocular pain need ophthalmological assessment. Non-specific conjunctivitis seldom requires treatment and usually diminishes in intensity with subsequent

exposures to alendronate. However, alendronate may need to be discontinued for other ocular inflammation to resolve; this is always necessary for scleritis.²

Myalgia and arthralgia common; synovitis rare but can be severe

In clinical trials approximately 4% of patients treated with alendronate 10mg daily developed muscle, bone or joint pain compared with 2.5% of patients receiving placebo. These reactions were rarely severe. The time to onset varied from one day to several months after starting treatment. Recovery was usual when alendronate was discontinued. Recurrence in patients re-challenged with alendronate or another bisphosphonate has been reported.¹ In some patients myalgia has occurred as part of an influenza-like syndrome that occurs in the early phase of treatment, and manifests as fever and malaise.¹

CARM has received seven reports of patients experiencing synovitis while taking alendronate. Three patients experienced recurrence on re-challenge. In one, the synovitis was severe enough to cause carpal tunnel syndrome that required urgent decompression.⁴ There is one other report of severe myalgia and polyarthritis in the literature.⁵ If synovitis or polyarthritis occur, or there appears to be a flare of pre-existing arthritis, a trial withdrawal of alendronate is recommended.

Oesophagitis and oesophageal ulceration can also occur

Abdominal pain, nausea, vomiting, dyspepsia and diarrhoea have been frequently reported to CARM. Oesophagitis, stomatitis and pharyngitis have also been reported. More serious reports include oesophageal ulceration, oesophageal stricture, gastric ulceration and gastrointestinal haemorrhage.

Post-marketing studies have identified oesophageal disorders including oesophagitis, erosive oesophagitis and oesophageal ulceration as adverse reactions to alendronate. Gastric ulcer, gastritis and gastroduodenitis have also been attributed to alendronate.⁶ Serious consequences of oesophageal ulceration attributed to alendronate have included stricture and perforation.¹

Gastrointestinal adverse effects can be minimised

Patients should be advised to swallow alendronate tablets whole with a full glass (at least 200ml⁷) of plain water after rising for the day. Food should not be eaten until 30 minutes after taking alendronate. Patients should not lie down for at least 30 minutes and not until they have eaten their first food for the day.¹ Following this advice will not prevent all alendronate-induced oesophageal events,⁶ therefore, patients should be instructed to seek medical attention if they have retrosternal pain, difficulty or pain when swallowing, or new onset or worsening dyspepsia.¹ It is not clear if concomitant nonsteroidal anti-inflammatory (NSAID) use or previous upper gastrointestinal pathology increase the risk,⁶ but particular care should be taken with these patients.¹

Allergy and rashes are also seen with alendronate

Urticaria, bronchospasm, angioedema and laryngeal oedema have all been reported to CARM. A wide variety of skin exanthems have also been reported with no particular type predominating. Post-marketing events reported include photosensitivity rashes, pruritis and, rarely, serious skin reactions including Stevens Johnson syndrome and toxic epidermal necrolysis.¹

Inflammatory-type reactions may occur with other bisphosphonates

This article has focused on alendronate, which is an aminobisphosphonate. The intravenous agents pamidronate and zoledronate belong to this same chemical class of bisphosphonates, and have also been causally associated with musculoskeletal pain, influenza-like disorders and ocular inflammation.^{8,9} The oral agent etidronate has a different chemical structure, lacking an amino group.¹⁰ Bisphosphonates lacking an amino group do not appear to cause oesophageal inflammation. Conjunctivitis is the only ocular inflammation that has been reported with etidronate.²

Other adverse reactions to alendronate

In addition to inflammatory adverse reactions to alendronate, other reactions are described in the Fosamax[®] data sheet¹ including the recently recognised one of osteonecrosis of the jaw (ONJ). This problem is being observed in oncology patients, many of whom have been treated with high-dose monthly bisphosphonates such as pamidronate and zoledronate. A small number of such cases have been reported worldwide in association with alendronate use¹¹ – see boxed item on the next page for more information about ONJ.

Competing interests (author): none declared.

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Bisphosphonates and osteonecrosis of the jaw

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This is a new entity for most doctors. It refers to the development of areas of exposed, necrotic bone in either the mandible or maxilla, which persist for a number of months. This problem is being recognised in oncology patients, many of whom have been treated with high-dose monthly bisphosphonates. This is most commonly seen in those with metastatic breast cancer or with multiple myeloma. The possible association with the use of bisphosphonates has raised the issue as to whether this is a problem in those who use bisphosphonates for benign indications, such as osteoporosis and Paget's disease. There have now been some case reports of this phenomenon, although they constitute less than five percent of the total number of cases recorded. For instance, there have been about one hundred cases reported worldwide with alendronate in the context of twenty million patient-years of use of this medicine. The lesions seem to develop following major dental procedures, such as extractions or dental implants, although they are sometimes associated with local trauma from dentures. Some dentists are recommending such procedures are entirely avoided in those with a history of bisphosphonate use. To many working in the field, this seems an over-reaction to what is, outside the context of oncological practice, a very rare event. While the pathogenesis and aetiology of this condition are being further explored, it does seem cautious to carry out any planned major dental procedures *before* individuals start on bisphosphonates. However, it must be borne in mind that substantial delays to the initiation of bisphosphonate therapy in those at a substantial risk of fracture will lead to the occurrence of preventable fractures.

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There is increasing evidence that leflunomide alone or in conjunction with methotrexate can cause pneumonitis, an acute respiratory illness characterised by dyspnoea, hypoxia and lung infiltrates. Prompt recognition is important as pneumonitis may be fatal or cause persisting disability. Early symptoms usually include dyspnoea but may be non-specific. Evaluation of baseline pulmonary status prior to treatment should be considered. Inform all patients of initial warning symptoms so that these can be investigated immediately and the suspect medicines discontinued.

Pneumonitis with leflunomide can have serious consequences

Leflunomide (Arava[®]) is a disease-modifying anti-rheumatic agent (DMARD) with anti-inflammatory and immunomodulating properties. It is indicated for the treatment of rheumatoid arthritis.¹ Clinical trials and post-marketing surveillance indicate that leflunomide can cause pneumonitis either as monotherapy or in conjunction with methotrexate, which is also known to cause this disorder.^{1,2}

Pneumonitis due to drug toxicity is an acute respiratory illness characterised by dyspnoea, hypoxia, and lung infiltrates. It is distinguishable from similar illnesses caused by infective organisms (e.g. *Pneumocystis carinii*) by an absence of organisms in blood, initial (induced) sputum cultures or bronchial wash/brush microscopy or cultures. Pneumonitis can be life-threatening, fatal or cause persisting respiratory compromise.³

Seven NZ reports of pneumonitis with leflunomide

The Centre for Adverse Reactions Monitoring (CARM) has received seven reports of pneumonitis occurring in patients taking leflunomide. All seven were taking methotrexate concurrently. There were four female and three male patients, aged 43 to 83 years. Initial symptoms were various combinations of dyspnoea, cough, fever, lethargy, weight loss and influenza-like symptoms followed by rapid progression to acute respiratory compromise. All patients had chest x-ray or computerised tomography (CT) evidence of lung infiltrates. Two

patients required ventilatory support in intensive care. Management consisted of discontinuation of leflunomide and methotrexate, treatment with oxygen or ventilatory support, and high-dose corticosteroids. Because leflunomide has a long half-life of one to four weeks,¹ cholestyramine was used to remove leflunomide in three patients with good effect. Five patients recovered, one died, and the other improved but had some persisting respiratory impairment.

Methotrexate itself can cause pneumonitis, usually within the first year of use.³ In the seven patients reported to CARM, the duration of leflunomide use prior to the onset of symptoms was 12 to 36 weeks. The duration of methotrexate use was usually longer and in four patients was greater than one year, thus supporting a causal role for leflunomide in the development of pneumonitis. These observations, together with similar reports from Australia, have been published.²

Pre-existing pulmonary disease and use of other DMARDs may increase the risk

By 2004, it was estimated that 400,000 people had received leflunomide worldwide, and the reported incidence of pneumonitis was 1 in 5000.⁴ However, in a post-marketing surveillance programme in Japan, 29 of the 3658 patients developed pneumonitis and 11 patients died.⁵ While not all cases may have been attributable to leflunomide, these observations suggest that the incidence of pneumonitis may be greater in clinical practice than in clinical trials. As with the New Zealand

patients, the Japanese patients frequently had past or present exposure to other DMARDs and some had pre-existing pulmonary disorders. It is possible that pre-existing pulmonary disease and other DMARDs, particularly methotrexate, may increase the likelihood of pneumonitis occurring with leflunomide. However, it should be borne in mind that many patients benefit from combination therapy where single agents have failed.

Inform all patients of early warning symptoms and consider baseline assessment

Clinical trials and the case reports to CARM indicate that leflunomide as monotherapy, or perhaps more commonly with methotrexate, can cause pneumonitis. Since patients with rheumatoid disease may have respiratory involvement or other lung disorders, a pre-treatment chest x-ray and evaluation of pulmonary status is useful in establishing a baseline should respiratory symptoms occur.

Patients should be informed of the early symptoms of pneumonitis and advised to seek medical attention promptly. New or worsening pulmonary symptoms need to be investigated without delay and leflunomide stopped, if appropriate.^{1,6} Methotrexate should also be discontinued if it is being taken concomitantly. Prescribers are reminded that monitoring for hepatic dysfunction and blood dyscrasias is also imperative in patients taking leflunomide.^{1,7} Additionally, please continue reporting leflunomide-associated adverse reactions to CARM.

Competing interests (author): none declared.

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Stilboestrol was prescribed for pregnant women in New Zealand up until the 1960s and long-term adverse effects are still being clarified. For daughters exposed *in-utero*, clear cell adenocarcinoma of the vagina and cervix continue to be observed rarely as these women reach their 50s, and there may be a second peak in later life. Mothers are at modestly increased risk of breast cancer, sons may be at increased risk of testicular cancer, and there are unconfirmed observations of third generation effects. Prescribers are reminded of the need to continue to monitor women exposed *in-utero*.

First evidence of transplacental carcinogenesis

Diethylstilboestrol (DES, known in New Zealand as stilboestrol; a synthetic oestrogen) was prescribed to about 1,000 pregnant women in New Zealand in the 1940s, 50s and 60s – in the belief it would reduce the risk of miscarriage.¹ In 1971 it was shown that daughters born to exposed mothers were at risk of clear cell adenocarcinoma (CCA) of the vagina. Since that time, other adverse effects have been documented in the daughters of women who took stilboestrol, as well as in the women themselves and their sons who were exposed *in-utero*.

Effects of stilboestrol persist

Although there has never been a systematic attempt to identify exposed women in New Zealand, publicity over the years has made many people aware of possible exposure. Most who think they have been exposed find that their medical records no longer exist. Therefore, clinicians need to be aware of the effects of stilboestrol, and of when the medicine was used, so that they can advise potentially affected mothers, daughters and sons appropriately. In the last 10 years – since the Ministry of Health last provided advice² – further research has clarified a number of issues. Hence it is timely to update practitioners and provide a reminder of ongoing monitoring recommendations.

Adverse effects include cancers and reproductive tract abnormalities

Exposed Mothers (i.e. women prescribed stilboestrol when they were pregnant)

Women who took stilboestrol during pregnancy have a modest increased risk of breast cancer of about 30% (corresponding to an extra 23 cases per 100,000 women per year). The risk of other cancers does not seem to be elevated.³

Exposed Daughters (i.e. women exposed to stilboestrol *in-utero*)

Clear cell adenocarcinoma of the vagina and cervix
This cancer occurs in about 1 in 1000 exposed daughters up to the age of 35 years,⁴ making the risk about 40 times that in the unexposed.⁵ The peak age of onset is late teens and early 20s, although cases have been reported in women up to their 50s.^{5,6} There is concern that there may be a second peak as these women age (there is a second age peak for diagnosis for CCA in non-exposed women in their 70s).⁷

Other Cancers

A possible increase in risk of breast cancer in exposed daughters has been reported, with a marginally significant elevation for women aged over 40 years.⁸ However, further investigation of all cancers in this combined cohort showed no increased risk of breast cancer or any other cancer apart from CCA.⁵ There has been a particular concern that stilboestrol might increase the

risk of squamous cell carcinoma of the cervix, but as yet there is no definitive answer. There is some evidence of an increase in high grade squamous intraepithelial neoplasia in exposed daughters, though this may be due to more intensive screening.⁹ Another cohort study with a low (and hence potentially biased) ascertainment of outcomes showed a three-fold increased risk of invasive cervical cancer among exposed daughters.¹⁰

Reproductive tract abnormalities

The following abnormalities are very common in stilboestrol-exposed daughters: vaginal adenosis, cervical ectropion, transverse cervical and vaginal ridges, hypoplastic uterus and a T-shaped uterus.¹¹ Recently, increases in paraovarian cysts,¹² endometriosis¹³ and uterine fibroids¹⁴ have been observed, but these associations are unconfirmed.

Reproductive function and pregnancy outcome

Primary infertility and pregnancy loss are both more common in exposed daughters.¹⁵ Long-term follow-up of stilboestrol-exposed daughters has confirmed an increased frequency of pre-term delivery, first trimester spontaneous abortion, second trimester pregnancy loss and ectopic pregnancy. Nevertheless among all exposed daughters in one cohort, 75% became pregnant and among these women 85% delivered at least one live full-term infant.¹⁶

Exposed Sons (i.e. men exposed to stilboestrol *in-utero*)

An increased risk of testicular cancer was suggested in earlier studies, but is not confirmed. The largest cohort study to date reported a two to three times elevation in risk amongst exposed sons, though this finding was not statistically significant.¹⁷ Abnormalities of the urogenital tract have been reported but study findings have been inconsistent.¹¹

Third generation effects (i.e. grandchildren of exposed mothers)

Studies in animals support the possibility of multi-generational carcinogenesis due to *in-utero* stilboestrol exposure.¹⁸ These effects have begun to be studied in humans. One cohort study

suggested an increased risk of hypospadias in the sons of exposed daughters.¹⁹ This finding has not been supported in a subsequent study.²⁰ Nevertheless both studies involved small numbers of exposed cases. A small study of third generation daughters, which included a detailed history and pelvic examination, showed that none of these granddaughters had changes usually associated with stilboestrol exposure.²¹

Monitoring recommendations for stilboestrol-exposed daughters

Women who may have been exposed to stilboestrol *in-utero* should be informed about the small risk of CCA of the vagina and cervix, and offered regular examinations. There are no specific New Zealand guidelines but the New Zealand Committee of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) advises clinicians to follow the advice of the US National Cancer Institute,²² which recommends the following annual examination:

- inspection of the vulva, vagina and cervix
- vaginal and cervical cytology
- vaginal and cervical palpation
- bimanual examination, including rectal examination.

This annual examination may be performed by a general practitioner. The part of the examination most important for detection of CCA is the examination of the vagina and cervix. Careful visual examination and palpation are essential. Cytological smears of the vagina (ideally taken as a circumferential sweep of the vaginal vault using the handle end of an Ayre's-type spatula²³) and cervix should be taken; although cases of CCA have been diagnosed in the presence of negative smears. If a grossly visible or palpable lesion is observed, referral to a gynaecologist for biopsy regardless of cytology results is advised.²² The New Zealand Committee of the RANZCOG can advise general practitioners of those gynaecologists practising colposcopy in their local area.

Exposed daughters who are planning a pregnancy, or are in early pregnancy, should be referred to an obstetrician. There are no specific monitoring requirements for women who took stilboestrol or their sons who were exposed *in-utero*.

Information is available for stilboestrol-exposed patients

Authoritative and well-presented information for affected mothers, daughters and sons is available on the following web sites:

- www.cdc.gov/DES
- www.DESfollowupstudy.org
- www.health.nsw.gov.au/des

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PRESCRIBING AND BUYING MEDICINE ON THE INTERNET – A RISKY BUSINESS

Medsafe Pharmacovigilance Team

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in December 2005. It is based on the 'Medicine and the internet' chapter authored by Stewart Jessamine and published in *Cole's Medical Practice in New Zealand* (2006 edition).

The advent of the internet has given rise to a new environment in which prescribers are presented with challenges beyond those encountered in the consulting room. Prescribers should be cautious when providing authorisation (such as a written prescription) to enable patients to obtain medicines over the internet. Prescribers should take into consideration factors such as the appropriateness of the medicine as well as safety and quality issues. Prescribers must also be aware that prescribing should only be for patients under their care and that prescribers are expected to provide the same standard of professional service to patients regardless of the communication method used.

The internet presents new challenges for prescribers

Due to increasing use of the internet by health consumers, it is inevitable that prescribers may be asked either to prescribe by e-mail for a patient, or to provide authorisation (such as a prescription) to enable a patient to obtain a medicine they have decided to buy over the internet. The current New Zealand legislation does not permit prescriptions to be issued by e-mail, so prescribers should avoid this activity. Additionally, in this country, it is illegal for consumers to be in possession of a prescription medicine unless it has been prescribed for them by a New Zealand-registered prescriber. Prescription medicines purchased over the internet enter the country by post and are subject to Customs inspection. Therefore, patients may be contacted and asked to provide evidence that a New Zealand-registered medical practitioner accepts responsibility for prescribing the medicine. While there are no legal barriers to prescribing to enable a patient to import a medicine purchased over the internet, this issue raises a number of ethical and practical questions.

Think twice about assisting patients to obtain medicines over the internet

There is a risk that medicines purchased on the internet may be counterfeit and therefore prescribers need to consider whether they are

prepared to facilitate patient access to a medicine delivered through the uncontrolled route of the internet before writing a prescription or providing authorisation. In coming to this decision, prescribers should consider whether the patient actually needs the medicine, and then consider if they are able to satisfy themselves that the medicine being imported meets the necessary standards of safety, quality and efficacy or in fact even contains the stated active ingredient. These are important considerations as a decision to facilitate access by providing a prescription or other authorisation may expose the medical practitioner to legal liabilities if harmful consequences arise from the patient's use of a medicine purchased on the internet. Prescribers who have queries about their legal liabilities and duty of care to patients in this situation should contact their medical indemnity organisation for advice. There are also guidelines provided by the New Zealand Medical Council (see www.mcnz.org.nz/portals/1/Guidance/Internet%20guidelines-revised2001.pdf).¹ It would also be reasonable to warn consumers against purchasing their medicines from internet sites based offshore due to the risk of poor quality or counterfeit products being supplied.² Consumers should be especially wary of web sites offering to provide prescription medicines without a prescription.

Know your legal and ethical responsibilities when prescribing for patients

The Medical Council of New Zealand's *Statement on the use of the Internet*¹ contains guidance on internet and electronic etiquette, and appropriate prescribing practices. This *Statement* is currently undergoing review by the Medical Council, who intend to strengthen the advice that prescribers are expected to provide patients with the same standard of care and prescribing practice regardless of the communication method or service delivery mechanism used by the prescriber.³ *The Medicines Regulations 1984* (section 39) clearly state that medical practitioners can only prescribe prescription medicines for patients under their care. Medsafe and the Medical Council interpret this as requiring a face-to-face consultation with the patient. In circumstances where the patient has previously been seen or examined by the doctor, prescribing should only occur if the doctor is confident that a physical examination would not add critical information about the management of the patient.¹

Don't risk prosecution – seek advice if in doubt

Medical licensing authorities such as the local Medical Council and the Federation of State Medical Boards of the United States Inc, as well as regulatory authorities including Medsafe, have indicated that they are prepared to prosecute doctors who provide internet-based medical services to patients not under their care. Medsafe has already successfully prosecuted a New Zealand-based company that was supplying prescription medicines without a prescription to consumers in the United States. Medsafe is also investigating several cases where doctors have signed, or countersigned, prescriptions for consumers located overseas so that the medicines could be dispensed from New Zealand pharmacies and posted back to the consumers. This activity is contrary to best medical and pharmacy practice, and the Medical Council's *Statement*. The recent decision by the Pharmacy Council to add a new clause to its *Code of Ethics* to prohibit pharmacists from selling medicines intended for the treatment of chronic diseases to patients outside of

New Zealand is a further example of how the health professions are no longer prepared to tolerate these activities.

Before embarking on any scheme to prescribe over the internet prescribers should take legal advice on the potential liabilities in both New Zealand law and in the law of the countries where their patients reside. Prescribers should also check that the terms of their medical practice (malpractice) insurance would cover them for care of patients in other countries.

Competing interests (authors): none declared.

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ADVERSE REACTIONS OF CURRENT CONCERN



The Medicines Adverse Reactions Committee (MARC) initiated the list of *adverse reactions of current concern* to bring particular medicine adverse reactions to the attention of prescribers. The intention is to encourage prescribers to report these reactions to the Centre for Adverse Reactions Monitoring (CARM) so that more information can be gathered, and further action taken if necessary. The reports provide a New Zealand perspective on emerging medicine safety issues.

As with any adverse reactions monitoring scheme, analysis can only be based on reports that are received. Prescribers are therefore encouraged to continue reporting adverse reactions to CARM so that the MARC can make the best possible recommendations based on information reflecting the New Zealand situation.

Please report **all cases** of the following adverse reactions to: CARM, NZ Pharmacovigilance Centre, PO Box 913, Dunedin. Use the reporting form inside the back cover of *Prescriber Update*, or download the form from the CARM or Medsafe web sites: www.otago.ac.nz/carm or www.medsafe.govt.nz/Profs/adverse.htm

Medicine/s	Adverse reactions of current concern	Prescriber Update reference
Complementary and alternative medicines*	all adverse reactions	Vol.23(2), July 2002 & No.13, Oct 1996
Leflunomide	all adverse reactions	Vol.25(1), May 2004 & Vol.26(2), December 2005 & This issue (see page 7)
Pioglitazone and Rosiglitazone	all adverse reactions	This issue (see below)

* includes herbal medicines, bee products, homoeopathic products, dietary supplements, minerals, and any other medicines containing animal or plant extracts.

Recent addition

Pioglitazone and Rosiglitazone – all adverse reactions

Serious and unexpected adverse reactions (such as macular oedema and congestive heart failure) associated with rosiglitazone use are being increasingly reported in the literature. It is possible that these are therapeutic class effects. Currently pioglitazone is fully funded and therefore likely to be prescribed more than rosiglitazone. For these reasons and so that more complete adverse reaction data can be gathered, all adverse reactions with pioglitazone or rosiglitazone are now included in the list of *adverse reactions of current concern*.

Recent deletion

SSRI antidepressants and severe agitation, severe restlessness/akathisia, and/or increased suicidality

The removal of these reactions has been recommended by the MARC due to a good level of prescriber awareness having been achieved. However, the MARC will continue to closely monitor these reactions, including regularly reviewing the published literature and overseas regulatory activity.

About the IMMP

The purpose of the Intensive Medicines Monitoring Programme (IMMP) is to identify previously unrecognised adverse reactions to new medicines. It also develops adverse reaction profiles for these medicines, as well as measuring incidence and characterising reactions of clinical concern. In addition, the IMMP is able to identify any high-risk groups amongst the patients being treated. The results of IMMP findings are used to enhance the safe use of medicines.

Which medicines are monitored?

Medicines of a new class may be added to the IMMP so that unknown adverse effects can be identified as soon as possible. Medicines may also be included in the programme if they are similar to other medicines for which safety concerns exist. The medicines currently being monitored are listed in the table below.

Medicines currently monitored by the IMMP

Medicine	Brand name/s
Clozapine	Clozaril, Clopine
Levonorgestrel intrauterine system*	Mirena
Olanzapine	Zyprexa
Quetiapine	Seroquel
Risperidone	Risperdal
Sibutramine*	Reductil

* New patients are no longer being added to the cohorts for these medicines because sufficient numbers of patients have already been recruited. However, follow-up of existing patients is continuing, which means that adverse event data are still being collected for these medicines. Therefore, prescribers may receive follow-up questionnaires asking about adverse events experienced by their patients taking an IMMP medicine. IMMP encourages prescribers to complete the questionnaires because their participation is a valuable contribution to patient safety.

What to report

Please report **all clinical events** in patients taking IMMP medicines, including:

- any suspected adverse reaction
- deaths (including cause if known)
- any new clinical events, even if minor or common
- accidents
- change in a pre-existing condition
- abnormal changes in laboratory test results
- possible interactions.

Where to report

Please report all adverse events occurring with IMMP medicines to: IMMP, NZ Pharmacovigilance Centre, PO Box 913, Dunedin. Use the reporting form inside the back cover of *Prescriber Update*, or download the form from either the NZ Pharmacovigilance Centre or Medsafe web sites: www.otago.ac.nz/carm or www.medsafe.govt.nz/Profs/adverse.htm

What to tell patients prescribed IMMP medicines

Please remember to tell patients that they have been prescribed a monitored medicine. This means the IMMP receives details of their prescriptions and that their doctor may be asked for clinical information on the patient's experience whilst taking this medicine. If possible, an explanatory IMMP leaflet should be given to the patient (available from the IMMP, NZ Pharmacovigilance Centre, PO Box 913, Dunedin).

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**Reporting form for Adverse Reactions
to Medicines, Vaccines and Devices
and all Clinical Events for IMMP**

PATIENT DETAILS

HP3442

Surname:		First Name/s:		NHI No:	
Address:		Date of Birth:		Sex:	
		Ethnicity:			

ALL MEDICINES IN USE *ASTERISK SUSPECT MEDICINE/S* Include over-the-counter (OTC) and alternative medicines

Medicine or Vaccine+batch no. (and brand name if known)	Daily Dose	Route	Date Started	Date Stopped	Reason for Use

DESCRIPTION OF ADVERSE REACTION OR EVENT

Date of onset: _____

Recovered Not yet recovered but improved Not yet recovered Unknown Fatal - Date of Death: _____

Severe? - Yes No Rechallenged? - No Yes Result: _____

OTHER FACTORS - Please tick or specify as appropriate

Renal disease Allergy : _____ Other Medical Conditions: _____

Hepatic disease Nutritional Suppl or OTC use : _____ Industrial Chemicals : _____

REPORTER - Please tick as appropriate: Doctor Pharmacist Dentist Nurse Other : _____

Name: _____

Address: _____ Signature: _____

Phone: _____ Date: _____

Send completed form to CARM

Freepost 112002, CARM, PO Box 913, Dunedin or Fax: (03) 479 7150



ADVERSE REACTIONS

What to report

Please report any suspect reaction of clinical concern. This includes adverse reactions involving:

- Prescription medicines
- Over-the-counter medicines (medicines purchased without a prescription)
- Complementary medicines (herbal medicines, naturopathic and/or homoeopathic medicines, and nutritional supplements such as vitamins and minerals)
- Vaccines.

In particular, please report the following:

- All suspected reactions to NEW medicines
- All Adverse Reactions of Current Concern¹
- All events to IMMP medicines²
- All suspected drug INTERACTIONS
- UNEXPECTED or SERIOUS reactions (including those suspected of causing death, admission to hospital, prolongation of hospitalisation, or birth defects)
- Serious ALLERGIC reactions (to enable a danger or warning to be entered in the national health database so re-exposure can be avoided for that individual).

How to report

Fill in the reporting form, which is available:

- overleaf (inside the back cover of *Prescriber Update*)
- from the CARM web site: <http://carm.otago.ac.nz/reporting.asp>

On-line reporting is also available on the CARM web site.

Where to report

Send all adverse reaction reports to CARM (Centre for Adverse Reactions Monitoring) in Dunedin.

Post to: Freepost 112002
 The Medical Assessor
 CARM
 University of Otago Medical School
 P O Box 913
 Dunedin

Fax: (03) 479 7150

Phone: (03) 479 7247

E-mail: carmnz@stonebow.otago.ac.nz

1. The list of *Adverse Reactions of Current Concern* is on page 14

2. The list of medicines in the Intensive Medicines Monitoring Programme (IMMP) is on page 15