ISSN 1172-5648

Prescriber Update

Vol. 29 No. 1
June 2008

A publication of

MEDSAFE
NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY
A BUSINESS UNIT OF THE MINISTRY OF HEALTH
www.medsafe.govt.nz

New Zealand Government

MINISTRY OF HEALTH
MANATŪ HAUORA

Prescriber Update is a member of the
INTERNATIONAL SOCIETY OF DRUG BULLETINS

www.medsafe.govt.nz

Resources available to you on the Medsafe web site, under the Health Professionals section:

- **Data sheets**
- **Prescriber Update articles**
- **Medicine classification issues**
- **Adverse reactions reporting forms**
- **Consumer Medicine Information (CMI)**
- **Media releases.**

www.medsafe.govt.nz

FROM THE EDITOR

Prescribers – don't miss out!

If you or your prescribing colleagues are not receiving these hard-copy issues of *Prescriber Update*, then forward your name and postal address to the Editor (contact details on page 20). There is no cost for joining the *Prescriber Update* mailing list and your details will be used only for this purpose. Pharmacists: please note that each pharmacy receives a copy of *Prescriber Update*.

Be the first to know

Any health professional can subscribe to receive e-mail notification of new *Prescriber Update* articles and other safety-related medicine information issued by Medsafe. To subscribe to this free service, go to www.medsafe.govt.nz/profs.htm and click in the centre of the screen where it says "Click here to subscribe to Prescriber Update Previews". Complete and submit your details to receive e-mails about new articles and safety information on the Medsafe web site.

Adverse events arising from brand-switches – report to CARM

Adverse events have been observed in some patients when switching from one brand of a medicine to another brand of the same medicine. Such brand-switch events may include decreased therapeutic efficacy, loss of symptom control, or development of previously non-apparent side effects. The Centre for Adverse Reactions Monitoring (CARM) in Dunedin asks that prescribers report these adverse events so patterns and trends can be identified, and brands of medicines investigated if necessary.

Please send brand-switch reports for any medicine to CARM, PO Box 913, Dunedin; fax 03 479 7150. Use the reporting form inside the back cover of this bulletin, 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 or medical device quality problems – please alert Medsafe

Prescribers and pharmacists are asked to inform Medsafe directly of problems with the quality or safety of medicines or medical devices as soon as they become apparent, so that remedial action can be taken, if necessary. Medsafe has the authority to request that pharmaceutical and medical device sponsors address problems with their products. Action may result in a product recall, issue of a warning to health professionals and consumers, field correction for medical devices, or action relating to the product specifications or manufacturing site.

If you are aware of any problem regarding the quality of a medicine or medical device, please report this in the first instance to the Compliance Management Branch (details below) at Medsafe who will investigate the matter. If the matter is serious or urgent, you should also contact the product sponsor, if possible.

For **medicine** quality issues: phone 04 819 6873

For medical **device** quality issues:
phone 04 819 6881 – If there is no response, please leave a voice message with a brief description of the problem and your contact details.

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.

ADR UPDATE

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 Rx ADVICE

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

Omeprazole and headaches

Headaches are a common adverse effect of omeprazole. Headaches can be difficult to diagnose in children and may present as prolonged or worsening irritability. Therefore, prescribers should consider headaches as a possible explanation in children with non-specific irritability who are taking omeprazole.

Tamoxifen and visual changes – investigate promptly

Retinopathy and keratopathy are recognised adverse effects of tamoxifen. While retinal damage more usually occurs at high doses used for a long duration, it has been reported in patients receiving standard doses of tamoxifen for only nine months. Patients should be asked to report the following symptoms of ocular damage without delay: blurred vision lasting more than a week, or change in colour vision. Any patients taking tamoxifen, regardless of dose or duration, who develop changes in visual acuity should be referred for ophthalmological examination. If tamoxifen is withdrawn promptly, the vision usually returns to normal without permanent impairment.

Amiodarone and lung toxicity – ongoing patient monitoring required

Prescribers are reminded that lung toxicity is the most serious potential adverse reaction associated with amiodarone therapy, and has a fatality rate of about 10%. Medsafe is aware that CARM and ACC have received a number of reports of lung toxicity in association with amiodarone use, in the last few years.

Prescribers are reminded that pulmonary function assessment (including chest X-ray) should be carried out at baseline and at 6-monthly intervals thereafter. Prescribers are advised of the importance of ensuring that a lead carer (either specialist or GP) is identified whenever amiodarone is prescribed. Liaison between specialists and GPs is vital to ensure that patient monitoring is carried out and any adverse effects are appropriately managed.

Roxithromycin-warfarin interaction of increased INR

Prescribers are reminded that there is an established but unpredictable interaction between erythromycin and warfarin, resulting in an increased international normalised ratio (INR).

CARM has received several reports of a possible interaction between roxithromycin and warfarin, with a resultant increased INR. These reports suggest that roxithromycin may have a potentiating effect on warfarin, but to a considerably lesser degree than erythromycin. This effect may, however, become clinically significant in patients receiving polytherapy, or in those who are elderly or otherwise at risk of increased sensitivity to warfarin. Therefore, in patients receiving warfarin, the INR should be closely monitored during the addition and withdrawal of concurrent treatment with roxithromycin.

Use of clozapine in older people requires extra care

Clozapine is only licensed for treatment-resistant schizophrenia. Its use for other indications requires informed consent. Use of clozapine in older patients carries a higher risk of adverse reactions such as postural hypotension, falls, sedation, and constipation, compared to use in younger patients. Therefore, increased clinical monitoring of the elderly is necessary to ensure their safety.

Myocardial infarction with glitazones

Recent literature supports an association between rosiglitazone and myocardial infarction. As pioglitazone belongs to the same class of medicines, it is possible pioglitazone may have a similar effect. However, no increase in the risk of myocardial infarction has been demonstrated for pioglitazone in published studies. The data are limited and further studies are needed. Meanwhile, the possibility of myocardial ischaemia with glitazones should be borne in mind when prescribing rosiglitazone or pioglitazone.

Update on cough and cold products

Following the commencement of a review of the safety of cough and cold products in children, by the FDA in the United States, the Medicines Adverse Reactions Committee (MARC) discussed this issue at their December 2007 meeting. The MARC subsequently recommended that all cough and cold medicines be contraindicated in children under two years of age. The rationale being that there is very limited evidence for efficacy in this age group; an absence of evidence-based dosage advice; and evidence of significant toxicity in overdose. As a result, the risk-benefit profile for the use of cough and cold medicines in children under 2 years of age is considered to be unfavourable. Medsafe and the MARC are currently considering the safety and efficacy of cough and cold medicines in children over two years of age.

Imiquimod cream – skin pigmentation changes and flu-like symptoms

Use of imiquimod (Aldara) cream can cause intense local inflammatory reactions. While these are rare, they can occur after only a few topical applications. These reactions may be accompanied, or even preceded, by flu-like systemic signs and symptoms such as malaise, pyrexia, nausea, and myalgias. An interruption of imiquimod use should be considered. In two cases reported to CARM, the patients had applied imiquimod more frequently than recommended for the condition being treated, and subsequently developed ulceration at the site of application.

Localised hypopigmentation and hyperpigmentation following the use of imiquimod cream may also occur. Follow-up information suggests that these skin colour changes may be permanent in some patients.

Concomitant parenteral administration of ceftriaxone and calcium

Prescribers are reminded of the potential risk of intravascular or pulmonary precipitations occurring due to the concomitant parenteral administration of ceftriaxone with calcium or calcium-containing solutions. Isolated neonatal deaths associated with calcium-ceftriaxone precipitates in the lungs and kidneys have been reported internationally. Although no reports have been received for patients other than neonates, the theoretical possibility exists for this interaction in patients of any age.

Ceftriaxone and calcium-containing solutions, including continuous calcium-containing infusions such as parenteral nutrition should not be administered to any patient, irrespective of age, within 48 hours of each other, even via different infusion lines at different sites. The data sheets for all ceftriaxone products available in New Zealand have been updated to include this warning. Prescribers are also reminded that ceftriaxone is contraindicated in hyperbilirubinaemic neonates.

Memory loss and depression with lipid-lowering agents

Prescribers are reminded that the risk of psychiatric reactions associated with lipid-lowering agents is not limited to statins. The symptomatic onset of psychiatric reactions, particularly memory loss and depression, can occur within days after initiation of treatment with statins, fibrates, or ezetimibe.[1] Reports have been received where the symptoms occurred within four days after commencing treatment with ezetimibe.[2] However, reactions can occur up to one year after initiation of treatment. In most reported cases, the symptoms resolved upon discontinuation of treatment. It is suspected that memory loss and depression are due to a reduction of brain cell membrane cholesterol, rather than direct adverse effects of the lipid-lowering agents themselves.[1]

It is important that patients are advised to inform their prescriber immediately if they experience symptoms suggestive of depression, memory loss, or other psychiatric reactions. Prescribers should consider the lipid-lowering agents as a possible causal explanation in patients presenting with psychiatric symptoms, particularly memory loss or depression.

References

1. Tatley M, Savage R. Psychiatric reactions with statins, fibrates and ezetimibe. *Drug Safety* 2007:30(3):195-201.
2. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Ezetimibe and depression – a possible signal. *Aust Adverse Drug React Bull* 2006;25(5):19. www.tga.gov.au/adr/aadrb/aadr0610.htm

Codeine in breastfeeding – risk of fatal infant morphine toxicity

Codeine is commonly used by breastfeeding women to treat mild to moderate pain associated with delivery. A report published in the *Lancet* in 2006[1] detailed the death from a morphine overdose of an otherwise healthy 13-day-old breastfed baby whose mother had been prescribed codeine (60mg bd for 2 days and then 30mg bd thereafter) to treat episiotomy pain. The baby experienced feeding difficulties and lethargy at day 7, and was found dead on day 13. Analyses of the baby's blood and the mother's breast milk found toxic levels of morphine in both. Subsequent genetic testing of the mother determined that she was an ultra-rapid metaboliser (URM) of codeine, which explained the very high levels of morphine.[1]

The chance of being an ultra-rapid metaboliser of codeine varies amongst different racial groups.[2] It is estimated that approximately 1-10% of Caucasians are URMs;[2] it is unknown what proportion of Maori or Pacific people are URMs of codeine. However, in the absence of genetic testing, it is not possible to identify URMs prior to prescribing codeine.

Therefore, prescribers are advised to carefully consider the risks and benefits before prescribing codeine for breastfeeding mothers. If codeine is prescribed, the lowest dose should be used for the shortest period of time. Patients should be advised of the symptoms of morphine toxicity in themselves (nausea, vomiting, somnolence, constipation and/or difficulty caring for the baby) and their babies (increased sleepiness – i.e. sleeping for more than 4 hours in the neonatal period, difficulty breastfeeding, breathing difficulties, or limpness). Patients should be advised to discontinue codeine and to seek medical attention immediately if these symptoms occur.[3]

References

1. Koren G, et al. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet* 2006;368:704.
2. FDA Public Health Advisory: Use of codeine by some breastfeeding mothers may lead to life-threatening side effects in nursing babies. August 2007. www.fda.gov/cder/drug/advisory/codeine.htm and www.fda.gov/CDER/Drug/InfoSheets/HCP/codeineHCP.htm
3. Douglas Pharmaceuticals Ltd. *Codeine Phosphate data sheet*. 28 August 2007. www.medsafe.govt.nz/profs/datasheet/cCodeinePhosphatetab.htm

Graseby syringe driver update

In October 2007, the supply of Graseby MS-Series Syringe Drivers was ceased in New Zealand, due to safety concerns. These syringe drivers are commonly used in palliative care and other situations to provide continuous ambulatory infusion of medicines. Spare parts and servicing for existing devices continues to be available through Smiths Medical.

Regulators in several countries, including Australia and the UK, have previously issued safety alerts in relation to the Graseby MS-Series Syringe Driver; and these have related to possibilities of over-infusion, tampering with the device, and confusion between the different models of Graseby device.

Medsafe is cognisant of the clinical implications of the decision to cease supply. It therefore did not require the existing devices to be recalled or withdrawn from clinical use where alternates are not available, provided the manufacturer's instructions for the Graseby MS-Series Syringe Drivers are carefully observed.

Medsafe also recognises that there are on-going risks associated with these devices and therefore advises users to give immediate consideration to sourcing alternative equipment which meets the Global Harmonisation Task Force (GHTF) "Essential Principles" of safety and performance (www.ghtf.org/documents/sg1/sg1n41r92005.pdf).

A Syringe Driver Advisory (SDA) group has been established in New Zealand to facilitate the safe and smooth transition from the use of Graseby syringe drivers to alternative device(s). The SDA group recognises the need to plan for changing over to a different device; and that current users are providing generalist or specialist palliative care in a variety of settings, or within a variety of pediatric and neonatal healthcare settings. This has practical, financial and educational implications. The SDA group wishes to provide a supportive, rather than a directive role. More details about the SDA Group, and background information about the reasons for ceasing distribution of Graseby syringe drivers, are available on the Medsafe web site (www.medsafe.govt.nz/profs/device-issues.asp).

TUMOUR NECROSIS FACTOR INHIBITORS – RECOGNISE AND TREAT INFECTION PROMPTLY

ADR UPDATE

Ruth Savage, Senior Medical Assessor, New Zealand Pharmacovigilance Centre, Dunedin

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in May 2008.

Serious infections, such as pneumonia, sepsis and tuberculosis (TB), have been reported in patients using the TNFα inhibitors: adalimumab, etanercept, or infliximab. The infections can be severe and progress rapidly, leading to fatalities in some instances. Reactivation of TB or hepatitis B can also occur. Prescribers should consider infection in patients taking TNFα inhibitors who present with unexplained illness. Dental abscesses have been the likely initial source of infection in two NZ case reports. Early recognition with prompt treatment of any infection in patients taking TNFα inhibitors is essential to prevent the development of life-threatening or fatal sepsis.

TNFα inhibitors are potent immunosuppressants used for severe inflammatory diseases

Three tumour necrosis factor alpha inhibitors (TNFα inhibitors) are approved for use in New Zealand: adalimumab, etanercept, and infliximab. These medicines are potent immunosuppressants, and are indicated for severe forms of rheumatoid arthritis (RA) and other conditions such as psoriatic arthritis, ankylosing spondylitis, and psoriasis.[1-3]

Serious infections including pneumonia, sepsis, tuberculosis (TB), reactivation of tuberculosis and other opportunistic infections, some of which have been fatal, have been reported with TNFα inhibitors.[1-3] Reactivation of hepatitis B in chronic carriers can also occur.[4] Patients taking TNFα inhibitors have severe inflammatory disease and are already at increased risk of infection with co-morbidities and other immunosuppressant agents contributing.[5]

Studies support an increased risk of infections

One longitudinal non-randomised study comparing patients with RA taking TNFα inhibitors (7664) with those taking disease modifying anti-rheumatic drugs (DMARDs) without TNFα inhibitors (1354) found no significant increase in the incidence of serious infection overall, but a significantly greater incidence of skin and soft tissue infections (11.9 v 3.0/1000 patient-years).[6] However, when the analysis was confined to the first 90 days after commencing a TNFα inhibitor, the risk of serious infection increased four-fold compared with users of DMARDs alone (72.2 v 24.4/1000 patient-years).[7] Tuberculosis occurred in patients (ten) exposed to TNFα inhibitors but not those exposed only to DMARDs. In more cases than expected, the TB was extrapulmonary.[6] In a study of serious infections associated with TNFα inhibitors, the majority were pneumonias, followed by cellulitis and soft tissue infections, and renal/urinary tract infections.[5]

Severity and rapid progression of infection requires expedient action

The rapid progression and severity of infections occurring in patients taking TNFα inhibitors also needs to be considered. CARM reports for adalimumab and infliximab indicate that infection developing in patients taking these agents can rapidly become disseminated and profound, leading to life-threatening or fatal sepsis. It is, therefore, important to treat any infection occurring in patients taking TNFα inhibitors at an early stage, even if it appears minor. Dental abscesses appear to have been the initial source of infection in two of the cases reported to CARM. It is also important to include infection, including opportunistic infection, in the differential diagnosis of patients presenting with unexplained illness; for example, an elderly patient presenting with confusion who had encephalitis due to toxoplasmosis. TNFα inhibitor treatment should be discontinued if serious infection occurs.[1-3]

Monitor patients during and after treatment with TNFα inhibitors

Product information for the TNFα inhibitors available in New Zealand clearly outlines the steps for infection screening and management prior to initiating treatment, which is by a specialist.[1-3] During treatment, it is important to respond promptly to presentations suggestive of infection and to monitor patients at risk of TB or hepatitis B reactivation. This also applies after treatment has been discontinued as the immunosuppressant effect of TNFα inhibitors may persist for several months.[1-3]

Competing interests (author): None declared.

References

1. Abbott Laboratories (NZ) Ltd. *Humira (adalimumab) data sheet*. 22 January 2008. www.medsafe.govt.nz/profs/datasheet/h/Humirainj.htm
2. Schering-Plough. *Remicade (infliximab) data sheet*. 5 October 2007. www.medsafe.govt.nz/profs/datasheet/r/Remicadeinj.htm
3. Wyeth Consumer Healthcare Pty Limited. *Enbrel (etanercept) data sheet*. 12 March 2008. www.medsafe.govt.nz/profs/datasheet/e/Enbrelinj.htm
4. Medsafe. *Hepatitis B reactivation associated with the anti-TNF agents, Enbrel (etanercept), Humira (adalimumab) and Remicade (infliximab)* – letter sent to specialists. 8 November 2006. www.medsafe.govt.nz/profs/PUarticles/HepBLtr.pdf
5. Curtis JR, Patkar N, Xie A, et al. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. *Arthritis & Rheumatism* 2007;56:1125-1133.
6. Dixon WG, Watson K, Lunt M, et al. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy. Results from the British Society for Rheumatology Biologics Register. *Arthritis & Rheumatism* 2006;54:2368-2376.
7. Dixon WG, Symmons DPM, Lunt M, et al. Serious infection following anti-tumour necrosis factor therapy in patients with rheumatoid arthritis. Lessons from interpreting data from observational studies. *Arthitis & Rheumatism* 2007;56(9): 2896-2904.

SSRI USE IN PREGNANCY – COLLABORATIVE DECISION-MAKING IS KEY

MARC Rx ADVICE

Medsafe Editorial Team

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in May 2008.

Recent studies suggest that SSRI antidepressant use in pregnancy may increase the risk of congenital abnormalities. There is also evidence to suggest that use of these medicines in later stages of pregnancy can lead to neonatal complications indicative of a withdrawal syndrome, and to persistent pulmonary hypertension of the newborn. As untreated depression can adversely affect maternal and foetal well-being, decisions about the treatment of depression in pregnant women may be challenging for healthcare professionals and patients. Prescribers are encouraged to discuss the potential benefits and risks of antidepressant treatment with patients who are pregnant or are contemplating pregnancy.

Prenatal exposure to SSRIs associated with increased risk of adverse pregnancy outcomes

Selective Serotonin Reuptake Inhibitors (SSRIs) are licensed in New Zealand for the treatment of depression, anxiety, and obsessive-compulsive disorders. Recent evidence suggests that the use of these medicines in pregnancy may be uncommonly associated with an increased risk of adverse effects in the newborn.[1-6]

Possible increased risk of congenital malformations with first trimester exposure

Recent studies have raised concerns about a possible association between maternal use of SSRIs and an increased risk of congenital malformations. These include cleft palate, hypospadias, and cardiovascular abnormalities such as septal defects.[1-3] Data suggest that the risk of birth defects for women with first trimester paroxetine exposure may increase from 3% to around 4% for all congenital malformations, and from 1% to around 2% for congenital cardiac abnormalities. In studies of paroxetine, the majority of abnormalities observed have been cardiovascular in nature, of which ventricular septal defects were the most common.[1,3] As yet, there is insufficient evidence to ascertain whether the risk of such congenital abnormalities is lower with other antidepressants.

Whether this observed increase in risk is attributable to SSRIs or to other confounding factors requires further analysis. Nonetheless, this new research suggests there may be an association between SSRIs and congenital malformations; this appears to be strongest for paroxetine and club foot, neural tube defects and cardiovascular abnormalities.[4]

Risk of neonatal complications following exposure in later stages of pregnancy

Complications in the acute neonatal period have been reported in association with maternal use of paroxetine and other SSRIs in the later stages of pregnancy.[5-8] In some instances, the reported symptoms have been described as neonatal withdrawal syndrome, characterised by convulsions, irritability, excessive crying, and tremor.[5,9] Other reported clinical findings have included respiratory distress, cyanosis, apnoea, hyperreflexia, lethargy, somnolence, temperature instability, feeding difficulties, hypoglycaemia, and muscle tone abnormalities.[8,9]

In a recent case-control study, maternal use of SSRIs after the first 20 weeks of pregnancy was associated with an increase in the risk of persistent pulmonary hypertension of the newborn (PPHN).[7] Further investigation of this association is warranted; however, on the basis of this study, the absolute risk of PPHN among those who use SSRIs late in pregnancy is approximately 6 to 12 per 1000 women. This compares to 1 to 2 cases of PPHN per 1000 women in the general population.[7,8]

Patient-physician discussion about risks and benefits of antidepressant treatment during pregnancy is key

Decisions surrounding minimisation of risk to the foetus while limiting morbidity from untreated maternal depression may be challenging, and should be made collaboratively with the patient. Prescribers are therefore encouraged to discuss the potential benefits and risks of antidepressant treatment during pregnancy with female patients of child-bearing age. If a patient receiving SSRI antidepressant therapy is pregnant or planning to become pregnant, her history should be reviewed and options considered. The risk of foetal exposure to antidepressant medication, untreated maternal depression, and depressive relapse associated with discontinuation of maintenance treatment should be discussed. General Practitioners may wish to seek an expert opinion from a relevant specialist. rescribers should be particularly vigilant when reviewing ultrasound images for pregnant women who are taking an SSRI, and if necessary arrange for maternal serum alpha-fetoprotein levels to be checked.[9]

If a decision is taken to discontinue antidepressant treatment, or switch to another antidepressant, prescribers are reminded that this should be done in accordance with the prescribing information for the medicine to avoid possible withdrawal effects. In addition, as untreated depression can adversely affect maternal and foetal well-being, patients should be closely observed for depressive relapse if antidepressant treatment is stopped.[10,11]

Competing interests (authors): none declared.

References

1. GlaxoSmithKline Clinical Trial Register. Epidemiological Study: Updated preliminary report on bupropion and other antidepressants, including paroxetine, in pregnancy and the occurrence of cardiovascular and major congenital malformation. http://ctr.gsk.co.uk/summary/paroxetine/studylist.asp 13 December 2005.
2. Wogelius P, Norgaard M, Gislum M, et al. Maternal use of selective serotonin reuptake inhibitors and risk of congenital malformations. *Epidemiology* 2006;17(6):701-704.
3. Kallen B. Antidepressant drugs during pregnancy and infant congenital heart defect. *Reproductive Toxicology* 2006;21:221-222.
4. Louik C, Lin AE, Werler MM, et al. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. *NEJM* 2007;356(26):2675-2683.
5. Sanz E, de Las Cuevas C, Kiuru A, et al. Selective serotonin reuptake inhibitors in pregnant women and neonatal withdrawal syndrome: a database analysis. *The Lancet* 2005;365:482-487.
6. Oberlander T, Warburton W, Misri S, et al. Neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitor antidepressants and maternal depression using population-based linked health data. *Archives of General Psychiatry* 2006;63:898-906.
7. Chambers C, Hernandez-Diaz S, Van Marter L, et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *New England Journal of Medicine* 2006;354(6):579-587.
8. GlaxoSmithKline NZ Limited *Aropax (paroxetine) data sheet* 2 June 2006. www.medsafe.govt.nz/profs/Datasheet/a/Aropaxtab.htm.
9. Mitchell LE, Adzick NS, Melchionne J, et al. Spina bifida. *Lancet* 2004;364(9448):1885-95.
10. Nonacs R, Cohen L. Assessment and treatment of depression during pregnancy: an update. *Psychiatric Clinics of North America* 2003;26(3):547-562.
11. Cohen L, Altshuler L, Harlow B, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *JAMA* 2006;295(5):499-507.

IMPULSIVE BEHAVIOURS WITH DOPAMINE AGONISTS

ADR UPDATE

Barry Snow, Neurologist, Department of Neurology, Auckland Hospital

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in May 2008.

Impulse control disorders such as pathological gambling and hypersexuality can occur in patients taking dopamine agonists for Parkinson's disease. Due to the unusual nature of these behaviours, often an association is not made with the medicine. High doses and dose increases of dopamine agonists can trigger the development of impulsive behaviours. Patients and their family/caregiver should be alerted to the possibility of these reactions and encouraged to seek help from their doctor if they notice unusual behaviours.

Some people with Parkinson's disease develop bizarre behaviours when taking dopamine agonists. This first came to attention when people taking pramipexole started to gamble pathologically. This was such an unusual side effect that it took some time to associate the pathological gambling with the medicine. Since that time, it has become apparent that patients taking other dopamine agonists, such as ropinirole (Requip), pergolide (Permax), bromocriptine (Parlodel) and lisuride (Dopergin), can also develop this disorder. There have been very few cases of pathological gambling reported with levodopa alone.

Pathological gambling is part of a spectrum of disorders known as impulse control disorders or dopamine dysregulation syndrome. Other compulsions can include compulsive shopping, eating, and increased sexuality. The dopamine system, as well as controlling movement, is associated with reward. It seems likely that dopamine agonists can cause patients to feel rewarded by these excessive behaviours. The impulsive behaviours are bizarre, often embarrassing and shameful. For this reason, patients may not associate their behaviours with the medicine; or they may feel ashamed and not discuss them with their doctors, or hide them from their families.

The frequency of these disorders has been reported as between 2.8% and 8% of patients with Parkinson's disease who are taking dopamine agonists. This compares with about 1% in the general population. The actual prevalence may be higher than previously thought because of the potential concealment by patients. Risk factors for pathological gambling include being young, male, and having psychiatric co-morbidity. High doses increase the risk of gambling, and patients may develop the disorder shortly after an increase in the dose of their dopamine agonist.

Dopamine agonists remain an important part of the therapeutic options for Parkinson's disease. Patients and their family or caregiver should be alerted about these potential problems, however, as they can have disastrous personal and financial consequences. There is no proven treatment for these impulse control disorders, but reduction or elimination of the dopamine agonist is obviously the first step. SSRI antidepressants may help control the impulsive behaviour.

Competing interests (author): none declared.

Address for correspondence: Department of Neurology, Auckland Hospital, Private Bag 92024, Auckland Mail Centre 1142.

Reference

Gallagher DA, O'Sullivan SS, Evans AH, et al. Pathological gambling in Parkinson's disease: Risk factors and differences from dopamine dysregulation. An analysis of published case series. *Movement Disorders* 2007;22(12):1757-1763.

CLOZAPINE AND ACHY BREAKY HEARTS (MYOCARDITIS AND CARDIOMYOPATHY)

ADR UPDATE

Medsafe Editorial Team

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in May 2008.

Clozapine can cause myocarditis, which may be fatal. It has also been associated with cardiomyopathy. While risk factors are unknown, pre-treatment cardiovascular screening is recommended. Myocarditis generally occurs one to two months after commencing clozapine; cardiomyopathy usually presents later, at around nine months. Common presenting symptoms of myocarditis include chest pain, tachycardia, and flu-like symptoms. These warrant immediate investigation and withholding of clozapine.

Clozapine-associated myocarditis is uncommon but serious

Prescribers are reminded that clozapine is associated with an increased risk of cardiac disorders, the most serious being myocarditis. While not a common adverse effect, clozapine-associated myocarditis can be fatal, affects relatively young people, can have a rapid onset, and is not necessarily dose-related.[1] In one published case series, fatalities occurred in 10.3% of the clozapine-treated patients who developed myocarditis.[1] Compared to the general population, clozapine-treated patients have a 17 to 322 times greater rate of myocarditis, and a 14 to 161 times greater rate of fatal myocarditis.[2]

The initial symptoms of myocarditis can be non-specific, such as tachycardia, fever, and flu-like symptoms.[3] The most probable mechanism is a medicine-induced, acute hypersensitivity (type 1, IgE-mediated) reaction, which may be part of a drug hypersensitivity syndrome.[2]

Cardiomyopathy also appears to be a risk associated with clozapine

To a lesser extent, clozapine has also been linked to cardiomyopathy. However, there is uncertainty if this is a consequence of myocarditis being unrecognised in the early stages, or whether cardiomyopathy is a clinically distinct and chronic cardiac disorder.[1,4]

Estimates of the incidence of clozapine-associated myocarditis range from 1 in 10,000 to 1 in 500 patients;[5] and for cardiomyopathy with clozapine, about 1 per 2000 patient-years.[4] True incidences are difficult to calculate due, in part, to the non-specificity of presenting signs and symptoms, and incomplete definitive diagnostic evidence, making interpretation of case reports complex.[5]

Characteristics of local cases reflect those reported in Australia

In New Zealand, 25 cases of clozapine-associated myocarditis[6] and 17 of cardiomyopathy were reported between March 2000 and November 2007. In the myocarditis case series, the median age of the patients was 30.5 years; 80% of cases had a time-to-onset of one month; and two patients died.[6] A similar pattern of reporting has been seen in Australia with 116 cases of myocarditis (including 12 deaths) and 90 cases of cardiomyopathy in association with clozapine use, reported during the January 1993-December 2003 time period.[1]

Risk factors remain elusive but dose probably not a contributor

To date, no clear risk factors have been identified for clozapine-associated myocarditis and cardiomyopathy. The rate of upward dose titration has been questioned as a possible contributor but there is no clear evidence to support this theory.[1] In one published case series, over 90% of the cases of clozapine-associated myocarditis reported a daily dosage range of 100-450mg, suggesting that dose is not necessarily a risk factor.[1]

Onset of myocarditis is often within the first month of clozapine treatment

Common presenting symptoms of clozapine-associated myocarditis include fever, dyspnoea, flu-like symptoms, tachycardia, and chest pain. Clinical findings commonly include ECG abnormalities, elevated creatine kinase (CK) and troponin levels, and eosinophilia. Most cases of myocarditis develop within one month of commencing clozapine treatment.[1,2] In comparison, cardiomyopathy usually has a more latent onset, at approximately nine months after starting clozapine.[3]

Conduct cardiovascular assessment before starting patients on clozapine

Pre-treatment cardiovascular screening should include a full history of pre-existing cardiac problems.[7] Use of clozapine in patients with severe cardiac disorders (e.g. myocarditis) is contraindicated.[8,9] There are guidelines for myocarditis which recommend baseline tests of ECG, and measurement of troponin (I or T), serum creatinine and eosinophils; then repeating ECG and troponin (I or T) at 7 and 14 days after starting clozapine; but these are not New Zealand-specific guidelines.[10] Consider repeating troponin (I or T) and ECG once full maintenance dose is achieved.[7] Echocardiography at six months has been suggested to screen for possible developing cardiomyopathy.[10] Prescribers should bear in mind that the sensitivity of CK for myocarditis may be very low,[10] and it is not known whether eosinophilia is a reliable predictor of myocarditis.[8,9]

Prescribers, patients and caregivers need to be vigilant during treatment

Tachycardia that persists at rest, accompanied by arrhythmias, shortness of breath or signs and symptoms of heart failure, may rarely occur during the first month of clozapine treatment and very rarely thereafter. The occurrence of these signs and symptoms necessitates an urgent diagnostic evaluation for myocarditis, especially during the titration period.[8,9]

The possibility of myocarditis should be considered in patients receiving clozapine who present with unexplained fatigue, dyspnoea, tachypnoea, fever, chest pain, tachycardia, palpitations, other signs and symptoms of heart failure, ECG changes (such as ST-T wave abnormalities) or arrhythmias – particularly during the first two months of clozapine treatment.[8,9] Patients taking clozapine and their caregivers should be advised to maintain vigilance (especially in the first two months) for the development of these symptoms which are suggestive of myocarditis and to see their doctor immediately if these occur.

Promptly investigate if suspicious and avoid re-exposure if diagnosis confirmed

Prescribers should have a high index of suspicion with a low threshold for cardiologist referral, especially in young patients without cardiac disease risk factors.[5,11] In patients where myocarditis is suspected, further doses of clozapine should be withheld and the patient referred urgently to a cardiologist for investigations; additionally, it may be useful for the GP to arrange an immediate ECG and troponin test, as this will inform the urgency of the cardiologist appointment and possibly also indicate if hospital admission is warranted.

If diagnosis of myocarditis is confirmed, clozapine treatment should be stopped and future exposure avoided.[7] Reporting such events to the Centre for Adverse Reactions Monitoring in Dunedin will ensure that a warning or danger alert is entered into the national Medical Warning System for that patient, so that the risk of re-exposure to clozapine can be avoided when the patient accesses health care in the future. If myocarditis is ruled out, consider other possible diagnoses such as cardiomyopathy.[1]

Competing interests (authors): none declared.

References

1. Haas SJ, Hill R, Krum H, et al. Clozapine-associated myocarditis: A review of 116 cases of suspected myocarditis associated with the use of clozapine in Australia during 1993-2003. *Drug Safety* 2007;30(1):47-57.
2. Adverse Drug Reactions Advisory Committee (ADRAC). Serotonin syndrome. *Australian Adverse Drug Reactions Bulletin* 2007;26(3).
3. Merrill DB, Dec GW, Goff DC. Adverse cardiac effects associated with clozapine. *Journal of Clinical Psychopharmacology* 2005;25(1):32-41.
4. Kilian JG, Kerr K, Lawrence C, Celermajer DS. Myocarditis and cardiomyopathy associated with clozapine. *Lancet* 1999;354:1841–1845.
5. Tanner M A, Culling W. Clozapine associated dilated cardiomyopathy. *Postgrad Med J* 2003;79:412–413.
6. Hill GR, Harrison-Woolrych M. Clozapine and myocarditis: a case series from the New Zealand Intensive Medicines Monitoring Programme. *NZMJ* 2008 [in press].
7. Personal communication, July 2007 and February 2008. Cardiologist, Wellington.
8. Novartis New Zealand Limited. *Clozaril (clozapine) data sheet* 2 October 2007. www.medsafe.govt.nz/profs/datasheet/c/Clozariltab.htm
9. Douglas Pharmaceuticals Ltd. *Clopine (clozapine) data sheet* September 2007. www.medsafe.govt.nz/profs/datasheet/c/Clopinetab.htm
10. Novartis Pharmaceuticals Australia Pty Ltd. *Clozaril and Myocarditis: Clinical Guidelines*. 16 December 1999.
11. Magnani JW, Dec GW. Myocarditis: Current trends in diagnosis and treatment. *Circulation* 2006;113:876–890.

LEFLUNOMIDE – UPDATE ON SERIOUS TOXICITY

ADR UPDATE

Ruth Savage, Senior Medical Assessor, New Zealand Pharmacovigilance Centre, Dunedin

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in May 2008.

Leflunomide is an effective disease modifying anti-rheumatic drug (DMARD). However, it can cause serious hepatic, haematologic, respiratory, and dermatologic adverse effects. Leflunomide is a potent immunosuppressant, reducing resistance to infection which, when it occurs, can be severe and disseminated. Tuberculosis reactivation has also been reported. There is evidence that leflunomide causes peripheral neuropathy, and presenting symptoms may mimic rheumatoid vasculitis. There is emerging evidence of a greater likelihood of pancytopenia, pneumonitis, and hepatotoxicity occurring when leflunomide is prescribed with methotrexate; these reactions have also been reported in patients taking leflunomide alone.

Serious infection and tuberculosis reactivation

Reports to CARM and published case reports include opportunistic infection, pneumonia, sepsis, other serious infections, and tuberculosis reactivation attributed to leflunomide.[1,2] In many of the CARM reports, patients were also taking other DMARDs, corticosteroids, or TNF alpha inhibitors[3] which, as well as severe rheumatoid arthritis itself, can also reduce resistance to infection.[1,2] It is important that infection is diagnosed and treated promptly in patients taking leflunomide as it is a potent immunosuppressant; and infection can become severe and difficult to control.[1,2]

Peripheral neuropathy presents with sensory changes

In a published case series from Australia, leflunomide was the sole suspect medicine in the 24 reports of peripheral neuropathy.[4] Onset was described as insidious, usually with sensory changes – a clinical picture that could be confused with rheumatoid vasculitis. Six patients improved on dechallenge, three after washout with cholestyramine. Several had not improved at the time of reporting. It is important to be aware that peripheral sensory changes may represent a potentially reversible reaction to leflunomide.

Pancytopenia, pneumonitis and hepatotoxicity with combination therapy

Using a combination of methotrexate and leflunomide has proved to be effective in some patients with rheumatoid arthritis.[5] Methotrexate, like leflunomide, is known to be hepatotoxic; and is a recognised cause of pancytopenia and pneumonitis. The combination appears to increase the likelihood of these toxicities occurring.

In a study of 30 patients taking methotrexate and leflunomide in combination, five patients (17%) developed an increase in hepatic transaminases to more than 3 times the upper limit of normal – an incidence greater than that usually observed with either medicine alone.[1,2]

Co-prescription of methotrexate has been noted in 9 of the 11 (82%) Australian reports[6] and in both of the New Zealand reports of pancytopenia attributed to leflunomide. In contrast, there was co-prescription of methotrexate in only 32% of all adverse reaction reports for leflunomide in the Australian database, and 38% in the CARM database. Estimates of the incidence of pancytopenia were approximately 1 in 4000 for leflunomide monotherapy, and 1 in 700 for leflunomide with methotrexate.[6]

A similar pattern was seen in the New Zealand and Australian databases in 12 reports of leflunomide-associated pneumonitis, a form of interstitial lung disease that can be rapidly progressive and fatal. Nine of these 12 patients (75%) were also taking methotrexate.[7]

Caution is advised whenever leflunomide is prescribed with other medicines known to be haemo- or hepatotoxic.[1,2]

Further information

Details of the reactions described, as well as other serious leflunomide adverse reactions, monitoring advice, and cholestyramine washout procedures can be found in previous *Prescriber Update* issues[8,9] and in the product data sheets for leflunomide.[1,2]

Competing interests (author): none declared.

References

1. Sanofi-aventis New Zealand Limited. *Arava (leflunomide) data sheet*. 3 July 2007. www.medsafe.govt.nz/profs/datasheet/a/aravatab.htm
2. AFT Pharmaceuticals Ltd. *AFT-Leflunomide data sheet*. 24 July 2007. www.medsafe.govt.nz/profs/datasheet/a/AFTLeflunomidetab.htm
3. Savage R. Tumour necrosis factor inhibitors: recognise and treat infection promptly. *Prescriber Update* 2008;29(1):5-6.
4. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Leflunomide and peripheral neuropathy. *Aust Adverse Drug React Bull* 2006;25(5):18-19. www.tga.gov.au/adr/aadrb/aadr0610.htm
5. Kremer JM, Genovese MC, Cannon GW, et al. Concomitant leflunomide therapy in patients with active rheumatoid arthritis despite stable dose of methotrexate: a randomized double-blind, placebo-controlled trial. *Ann Intern Med* 2002;137:726-733.
6. McEwen J, Purcell PM, Hill RL, et al. The incidence of pancytopenia in patients taking leflunomide alone or with methotrexate. *Pharmacoepidemiology and Drug Safety* 2007;16:65-73.
7. Savage RL, Highton J, Boyd IW, et al. Pneumonitis associated with leflunomide: a profile of New Zealand and Australian reports. *Internal Medicine Journal* 2006;36(3):162-165.
8. Medsafe Editorial Team. Leflunomide: serious multi-system adverse effects. *Prescriber Update* 2004;25(1):2-3.
9. Savage R. Leflunomide and pneumonitis. *Prescriber Update* 2006;27(1):7-8.

NON-SELECTIVE NSAIDS – CARDIOVASCULAR, SKIN AND GASTROINTESTINAL RISKS

MARC Rx ADVICE

Medsafe Editorial Team

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in May 2008.

The safety of non-selective non-steroidal anti-inflammatory drugs (non-selective NSAIDs) has been evaluated by the Medicines Adverse Reactions Committee (MARC). Non-selective NSAIDs do not differentiate between COX-1 and COX-2 in their inhibitory action, and are a separate class of drug to the COX-2 inhibitors. As part of their evaluation, the MARC reviewed adverse reaction reports received by the Centre for Adverse Reactions Monitoring (CARM) and the WHO (Vigibase), together with recently published literature and international regulatory activity.

Based on this review, the data sheets for all non-selective NSAIDs approved in New Zealand have been updated to include warnings about cardiovascular, skin and gastrointestinal risks, and to be consistent with revisions to the prescribing information in other countries.

Summary of changes to the NSAID data sheets

- After assessing the risk-benefit ratio in each individual patient, the lowest effective dose of an NSAID should be used for the shortest possible duration.
- Non-selective NSAIDs are associated with an **increased risk of serious cardiovascular events**, including cardiac failure, myocardial infarction and stroke, which may increase with dose or duration of use.
- Non-selective NSAIDs may lead to the **onset of new hypertension** or worsening of pre-existing hypertension. Patients taking anti-hypertensives with NSAIDs may have an impaired anti-hypertensive response. Blood pressure should be monitored closely during initiation of non-selective NSAID treatment and at regular intervals thereafter.
- Fluid retention and oedema have been observed in some patients taking NSAIDs; therefore, caution is advised in patients with fluid retention or heart failure.
- Non-selective NSAIDs can rarely cause **serious, potentially fatal, gastrointestinal effects** such as ulcers, bleeding and perforation, of which the risk may increase with dose or duration of use. These gastrointestinal effects can occur at any time without warning. If gastrointestinal bleeding or ulcers occur, NSAID treatment should be stopped immediately.
- The concurrent use of aspirin and non-selective NSAIDs increases the risk of serious gastrointestinal adverse events.
- Non-selective NSAIDs may rarely cause **serious adverse skin events** such as exfoliative dermatitis, toxic epidermal necrolysis and Stevens-Johnson syndrome, which can be fatal and occur without warning. These severe skin reactions are idiosyncratic and independent of dose or duration of use.
- Prescribers should warn patients about the signs and symptoms of serious gastrointestinal toxicity and skin reactions.

General advice on prescribing non-selective NSAIDs

- Use the lowest possible dose and regularly review the need for long-term treatment.
- Consider the potential harms and benefits of non-selective NSAIDs, taking into account individual patient profiles, particularly risk factors for gastrointestinal, cardiovascular and skin adverse reactions.
- Advise patients of the risks of harm with non-selective NSAID use, and the warning signs of serious adverse reactions, so that patients and prescribers can collaboratively manage the risks associated with non-selective NSAID use.

PIROXICAM – restricted range of indications

Prescribers are reminded of the following recent changes regarding the use of piroxicam. These restrictions are to manage the greater risks of gastrointestinal side effects and serious skin reactions associated with piroxicam compared to other non-selective NSAIDs.

- Piroxicam is no longer indicated for acute gout, primary dysmenorrhea, post-operative pain, acute musculoskeletal disorders, or acute post-traumatic disorders.
- Piroxicam should only be used as second-line treatment for the symptomatic relief of pain and inflammation in patients suffering from osteoarthritis, rheumatoid arthritis, or ankylosing spondylitis.
- Piroxicam should only be prescribed by doctors with experience in the diagnostic evaluation and treatment of osteoarthritis, rheumatoid arthritis or ankylosing spondylitis.
- The first prescription of piroxicam should be for two weeks only, to ensure that the patient is reviewed before further piroxicam is prescribed.
- Piroxicam is contraindicated in patients with a history of gastrointestinal disorders associated with bleeding, and those who have had skin reactions to other medicines.
- The dose of piroxicam should be limited to a maximum of 20mg per day and should be regularly reviewed.
- Piroxicam should always be used at the lowest effective dose (no more than 20mg per day) for the shortest possible duration.
- Combination therapy with gastro-protective agents should be carefully considered for all patients, particularly the elderly.
- Piroxicam should not be prescribed in combination with any other NSAID or anti-coagulant.

The data sheets for piroxicam products available in New Zealand have been updated to reflect these restrictions.

INTERNATIONAL NON-PROPRIETARY NAMES (INNs) FOR MEDICINES

Medsafe

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in November 2007. Also available at: www.medsafe.govt.nz/profs/RIss/INN.asp

What is an INN?

INN (international non-proprietary names) is a nomenclature system used to identify active ingredients of medicines. Each INN is a unique name that is internationally consistent and globally recognised. The INN system began operating in 1953 and is now administered by the World Health Organisation. The aim of the INN system is to provide health professionals with a unique and universally available designated name to identify each pharmaceutical substance. The existence of such a nomenclature assists in the clear identification, safe prescription and dispensing of medicines to patients; and facilitates communication and exchange of information among health professionals and scientists world-wide.[1] See www.who.int/medicines/services/inn/en/ for more information about INNs.

Does New Zealand use INNs?

New Zealand legislation requires medicine labels to include certain information, including specifying the active ingredients. The medicines legislation does not specify which nomenclature system is to be used to identify the active ingredients. There is a range of nomenclature systems in existence world-wide for active ingredients, including the BAN (British Approved Names), USAN (United States Adopted Names), AAN (Australian Approved Names), and INN. Medsafe has always accepted medicines and labelling that uses any of these nomenclature systems. New Zealand is a small market and due to economy of scale, the medicines supplied here are often batches of product produced or packaged for a larger or international market. If that other market is in a country that requires medicines to be labelled as INNs, then NZ is likely to receive INN-labelled medicines. Globally, medicine manufacturers are rationalising production and this can limit the range of products available for supply to New Zealand. Increasingly, countries with large markets (due to their population size), and thus a critical mass, have required medicine manufacturers to adopt the INN when labelling their medicines. As a result, New Zealand is receiving an increasing number of medicines labelled with INNs. However, the use of INNs is not new in New Zealand. Thyroxine has been labelled as levothyroxine since January 1998; and since May 1999, there has been an amoxycillin product labelled by the sponsor as amoxicillin.

What does it mean for pharmacists?

Pharmacists have a professional and ethical responsibility to accurately identify the medicine prescribed, whether it be a new active ingredient, a change of brand name, or a different spelling or nomenclature for an active ingredient. Lack of familiarity with a medicine name is not an acceptable reason for dispensing errors to occur. As part of their licensing and operating requirements, New Zealand pharmacies are required to have access to reference pharmacopoeias, such as Martindale, which list synonyms for active ingredients and can be used to check the name of a medicine when in doubt. Pharmacists also use these reference texts when patients from other countries need assistance with their medicines, which invariably have different brand names to those available in New Zealand.

Does the Medsafe web site include INNs?

Medsafe has amended the search function on the Medsafe web site so that data sheets and Consumer Medicine Information (CMI) can be searched for using any of the accepted synonyms for active ingredients. For example, while "furosemide" is the INN, a search using the synonym "frusemide" will also locate any medicines containing furosemide.

Medsafe is asking New Zealand sponsors to ensure consistent use of nomenclature between the medicine data sheet and the product label, with respect to specifying active ingredients.

Reference

1. World Health Organisation. *Guidance on INN*. Accessed online at www.who.int/medicines/services/inn/en/

ADVERSE REACTIONS OF CURRENT CONCERN

MARC Rx ADVICE

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.

Regular amendments to the list of reactions are made either in response to adverse events reported in New Zealand or international pharmacovigilance issues.

Please report **all cases** of the following adverse reactions to: CARM, NZ Pharmacovigilance Centre, PO Box 913, Dunedin 9054. 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.28(1), November 2007 & Vol.23(2), July 2002 & No.13, Oct 1996
Leflunomide	all adverse reactions	Vol.29(1), June 2008 & Vol.27(1), June 2006 & Vol.26(2), December 2005 & Vol.25(1), May 2004
Pioglitazone and Rosiglitazone	all adverse reactions	Vol.29(1), June 2008 & Vol.28(1), November 2007 & Vol.27(1), June 2006

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

INTENSIVE MEDICINES MONITORING PROGRAMME

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 medicine currently being monitored is: **Varenicline (Champix)**

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 9054. Use the reporting form inside the back cover of *Prescriber Update*, or download it 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 9054).

Prescriber Update is published and distributed by Medsafe in the interests of safer, more effective use of medicines, medical devices and methods of diagnosis and treatment.

Medsafe: New Zealand Medicines and Medical Devices Safety Authority
A business unit of the Ministry of Health.

Editor: Sarita Von Afehlt
Medsafe, PO Box 5013, Wellington 6145, New Zealand
Ph: (04) 819 6800 Fax: (04) 819 6806
E-mail: sarita_von_afehlt@moh.govt.nz

Medsafe web site: www.medsafe.govt.nz

Published with the permission
of the Director-General of Health

New Zealand Government

CARM
CENTRE FOR ADVERSE REACTIONS MONITORING

Fax: (03) 479 7150
Phone: (03) 479 7247

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 9054 **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 Concern[1]
- All events to IMMP medicines[2]
- 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
PO Box 913
Dunedin 9054

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 18
2. The list of medicines in the Intensive Medicines Monitoring Programme (IMMP) is on page 19