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FROM THE EDITOR

Using NHI numbers to improve patient safety

About the NHI and NHI numbers

The National Health Index (NHI) is a register of all health care users in New Zealand. It assigns a unique identification number (known as the NHI number) to each person. This number is used to bring together a person's health data such as biographical details and hospital discharge diagnoses. This enables health care providers to correctly identify the information belonging to the person requiring health care. The NHI number is sometimes referred to as the Hospital Number, and is always in the format of three letters followed by four numbers (e.g. ABC1234).

How NHI numbers can improve patient safety

The NHI number plays a key role in the reporting of adverse reactions to medicines and vaccines. Each adverse reaction report received by the Centre for Adverse Reactions Monitoring (CARM) in Dunedin undergoes evaluation by a medical assessor. The adverse reactions are assessed for severity and association. For those reactions that are severe, or are associated with incapacitating morbidity, or are life-threatening (e.g. anaphylaxis), CARM uses the NHI to enter either a warning or a danger alert into the 'Medical Warnings System' (MWS) against that individual's NHI number so that future exposure to the implicated medicine can be avoided. This means that the next time the patient accesses health care, for example at an A&E department, the alert will flash up against that patient's NHI number. The MWS system also gives reassurance to GPs that regardless of which hospital or other health care facility their patients present at, the NHI will show the medical alert for that individual. This provides downstream value for the patient by drawing attention to potentially unsafe medicine options. A facility also exists within the MWS to record information that may be relevant, for example, the patient is receiving streptokinase or has a significant medical condition.

This safety mechanism provided by the MWS is facilitated when the reporter supplies the patient's NHI number at the time of reporting the adverse reaction to CARM. Thus, prescribers are encouraged to include the NHI number on all adverse reaction reports sent to CARM. Also, the more detailed the clinical information is that the reporter submits the more it will enable a comprehensive medical alert be to entered, if appropriate, into the MWS resulting in a greater contribution to patient safety and health outcomes.

More information about the NHI is available on the Ministry of Health web site: www.nzhis.govt.nz/nhi/index.html

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. As part of our editorial policy, articles displaying either of these symbols have undergone independent peer review. During the development of an article, the pharmaceutical company supplying the medicine referred to in the article may be given the opportunity to comment on the draft.

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.

LEFLUNOMIDE: SERIOUS MULTI-SYSTEM ADVERSE EFFECTS

ADR UPDATE

Medsafe Editorial Team

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in April 2004.

Leflunomide is an effective disease-modifying agent for rheumatoid arthritis. Its use has been associated with significant and serious adverse reactions involving haematological, hepatic, immune, dermatological and respiratory systems. The long half-life of leflunomide may delay resolution of some of these reactions. However, regular monitoring and patient education of early warning signs can reduce morbidity.

Leflunomide indicated for rheumatoid arthritis

Disease-modifying anti-rheumatic drugs (DMARDs) are being increasingly used early in the course of active rheumatoid disease.[1] Leflunomide (Arava®) is a relatively new immunomodulatory DMARD indicated for the treatment of rheumatoid arthritis (RA). It is a pro-drug activated by metabolism in the gut wall and liver, and excreted by the renal and biliary systems.[2] The active metabolite has a long half-life (1-4 weeks[2]), which may contribute to adverse effects that persist, worsen or even appear after leflunomide has been stopped.[3,4]

International adverse reaction reports include serious events

Global exposure to leflunomide is estimated to be 662,302 patient-years, to date.[5] While leflunomide has demonstrated efficacy in some groups of patients with active RA, international post-marketing experience includes reports of serious adverse reactions in patients treated with leflunomide. Although confounding factors such as concomitant use of known hepatotoxic or haematotoxic medicines (e.g. methotrexate) are present in many of the reported cases, a causal relationship with leflunomide cannot be excluded.[3,4,6-8]

International adverse reaction reports associated with leflunomide include the following:

- **Hepatic** adverse reactions including 15 cases of liver failure (nine with fatal outcome).
- **Haematological** adverse reactions ranging from neutropenia, thrombocytopenia and thrombocytosis, through to severe pancytopenia.
- **Dermatological** adverse reactions including Stevens-Johnson syndrome, bullous eruptions and skin necrosis.
- **Respiratory** adverse reactions such as interstitial pneumonitis and pulmonary infiltration.
- **Immune response** impairments including reports of severe infections such as sepsis.

New Zealand experience with leflunomide is comparable

It is thought that between 500 and 1500 patients in New Zealand have been prescribed leflunomide, up to the end of 2003.[5] The adverse reactions reported in New Zealand for this medicine are similar to those seen internationally.

Examples of the more serious local cases include:

- Elevated hepatic enzymes, along with neutropenia, thrombocytopenia and diarrhoea.
- Sepsis leading to multi-organ failure and death; concomitant medicines were methotrexate, ketoprofen and triamcinolone.
- Hypersensitivity pneumonitis, resulting in life-threatening respiratory compromise. The patient was taking leflunomide and methotrexate but did not relapse when methotrexate was re-introduced.

- Multiple bullous eruptions occurring within three weeks of starting leflunomide, and resolving upon discontinuation.

Awareness and monitoring reduces the impact of adverse effects

Post-marketing experience with leflunomide estimates the frequency of severe hepatic, dermatological, respiratory, haematological and infection reactions as being less than 1 in 10,000 (i.e. very rare). However, some blood dyscrasias have been reported to occur at a frequency of between 1 in 1000 and 1 in 10,000 (i.e. rare).[2] Despite the serious adverse reaction profile of leflunomide, it is an effective DMARD. As with all medicines use of leflunomide requires an assessment of its risk and benefits on an individual patient basis. Prescribers should be aware that the concomitant use of other immunomodulating agents may have an additive effect, not only on improving symptoms of acute RA but also on the frequency and severity of adverse reactions.

To minimise the risk of serious blood and liver adverse reactions, all patients taking leflunomide should have their haematological and liver function monitored. Once a pre-treatment baseline is established, monitor monthly for the first six months, then every 6-8 weeks thereafter. Ongoing monthly monitoring is recommended if methotrexate is used concurrently.[2] Prescribers are advised to refer to the recently updated Arava data sheet[2] (available at www.medsafe.govt.nz/profs.htm) for comprehensive monitoring recommendations.

Patients should be informed of early warning signs of possible adverse reactions and asked to contact their general practitioner as soon as possible if they experience any of the following: easy bruising, tiredness, pallor, skin lesions or rashes, shortness of breath, or increased frequency/susceptibility to infection. If serious reactions occur, the long half-life of leflunomide's active metabolite may necessitate wash-out with an agent such as cholestyramine.[2]

Leflunomide has recently been added to the list of *Adverse Reactions of Current Concern* (see page 14). This means that prescribers are requested to report all leflunomide-associated adverse reactions to the Centre for Adverse Reactions Monitoring (CARM) in Dunedin – contact details are inside the back cover.

Competing interests (authors): none declared.

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MYOPATHY WITH STATINS: CHECK CK LEVELS AND INTERACTIONS

ADR UPDATE

Dr Ruth Savage, Medical Assessor; Dr Michael Tatley, Director, Centre for Adverse Reactions Monitoring, Dunedin

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Reports of myopathy and rhabdomyolysis with statins are a reminder to prescribers to measure creatine kinase (CK) levels in patients presenting with muscle pain or weakness. The risk of myopathy may be increased by high doses of statins, especially in patients with co-morbidities, or in the presence of interacting medicines such as diltiazem.

Myopathy known to occur with statins

While the statins are effective in providing protection from coronary and cardiovascular events, they are known to cause myopathy (usually dose-related) and, rarely, rhabdomyolysis.[1] A clinical diagnosis of myopathy is made when there is muscle pain or weakness accompanied by a creatine kinase (CK) level more than ten times the upper limit of normal. Rhabdomyolysis is a severe form of myopathy with muscle breakdown leading to myoglobinuria, which may result in renal failure and death.[2]

New Zealand reports of rhabdomyolysis

The Centre for Adverse Reactions Monitoring (CARM) has received eight recent reports (including two fatalities) of rhabdomyolysis occurring in patients taking between 20mg and 80mg of a statin daily. Six of these patients were taking simvastatin which, along with atorvastatin, is fully funded in New Zealand and therefore prescribed more often than the other available statins (i.e. fluvastatin and pravastatin). All patients in the eight cases initially complained of myalgia or muscle weakness and were later diagnosed with rhabdomyolysis. Two of the patients on simvastatin presented with urinary discoloration; one went on to develop acute renal failure. The duration to onset of symptoms ranged from 2-12 weeks from initiation of, or change in, statin therapy. The patients were between 54-79 years of age; five were taking other medicines known to interact with statins (i.e. four were taking simvastatin with diltiazem, and one bezafibrate with pravastatin). Three patients had significant co-morbidities including chronic renal failure and hepatic cirrhosis; two patients had recently had their simvastatin dose increased to 60mg and 80mg daily.

Monitoring helps improve outcome

It is advisable to monitor patients for signs and symptoms of muscle pain, tenderness or weakness, particularly during both the initial months of statin therapy and subsequent dose increases.[3,4] Creatine kinase measurements must be performed when symptoms occur. Patients with additional risk factors (e.g. diabetes, older age, hypothyroidism, liver or renal disease[1,5]) merit closer monitoring as they may be more at risk of rhabdomyolysis.[3]

Statin treatment should be discontinued immediately if an elevated CK level is found (i.e. CK >10 x upper limit of normal[6]), or where myopathy is suspected or diagnosed.[3,4] If there is a moderate rise in the CK level (i.e. 3-10 x upper limit of normal) then monitor CK levels weekly and seek specialist advice.[6] It is worth noting that measuring CK levels when statin therapy is initiated will provide a reference baseline; however, undertaking regular CK levels is probably not useful in the absence of therapy changes or the development of co-morbidity.[1]

Concomitant medicines may increase risk of myopathy

The risk of myopathy or rhabdomyolysis with simvastatin alone is dose related; the incidence, determined from clinical trials, is approximately 0.03% at 20mg, 0.08% at 40mg and 0.4% at 80mg daily. This risk is increased with concomitant fibrates, as they alone can cause myopathy.[3] The risk is also increased when simvastatin and atorvastatin (both CYP 3A4 substrates; fluvastatin and pravastatin are not[7]) are used concomitantly with potent CYP 3A4 inhibitors (eg. erythromycin, itraconazole, amiodarone, verapamil).[3,4] Diltiazem, a weaker inhibitor of CYP 3A4, is frequently prescribed with a statin. Diltiazem increases the risk of rhabdomyolysis to 1% when given with simvastatin 80mg daily.[3] However, fatal rhabdomyolysis has been reported in two New Zealand patients taking diltiazem whose simvastatin doses were increased to 40mg and 60mg daily, respectively. Both had significant co-morbidity.[8]

To minimise the likelihood of interactions, lower starting doses of simvastatin and atorvastatin should be used in patients already on fibrates, cyclosporin, amiodarone, verapamil, and other potent CYP 3A4 inhibitors.[3] Closer monitoring for signs and symptoms suggestive of myopathy is also recommended.[4] For patients already taking simvastatin or atorvastatin, the statin dose should be reduced when interacting medicines are prescribed. Diltiazem should not be co-prescribed with high doses of simvastatin or atorvastatin; and for all concurrent therapy, there should be closer monitoring. Consider temporarily discontinuing these statins if short-term courses of azole antifungals or macrolide antibiotics are required.[3] An alternative option would be to consider changing to pravastatin or fluvastatin.

Advise patients of warning symptoms

Prescribers should be aware that there is an increased risk of myopathy occurring in patients taking statins, and this risk may be further increased in the presence of co-morbidities or concurrent medicines. Patients who are prescribed statins need to be informed of the importance of promptly reporting unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.[3,4] Measure CK levels in patients who present with such symptoms. Where myopathy is suspected or diagnosed, immediate withdrawal of the statin is recommended.

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Correspondence to Dr Michael Tatley, New Zealand Pharmacovigilance Centre, PO Box 913, Dunedin.

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INHALED CORTICOSTEROIDS – WATCH FOR SKIN ATROPHY

ADR UPDATE

Marius Rademaker, Hon. Associate Professor, Dermatology Department, Waikato Hospital, Hamilton

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Inhaled corticosteroids can cause skin atrophy. This adverse effect may be exacerbated by sun exposure, possibly via a cumulative mechanism. The risk of skin atrophy can be minimised by using the lowest possible maintenance dose of inhaled steroid, as well as protecting the skin from sun exposure. Be aware that concurrent use of other forms of steroids can collectively increase the risk of skin atrophy and other steroid-induced unwanted effects.

Inhaled corticosteroids known to have some systemic effects

Inhaled corticosteroids have an essential role in the management of asthma. Inhalation allows high concentrations of corticosteroids to reach target sites within the lung while keeping systemic exposure to a minimum.[1] Although the safety profile of inhaled corticosteroids is generally superior to that of oral corticosteroids, systemic adverse effects do still occur.

A number of studies[2,3] confirm that inhaled corticosteroids, even at low doses,[4] can cause skin atrophy (i.e. paper-thin skin[5]) and purpura. The mechanism appears to involve a reduction in collagen synthesis.[4] In one study,[4] there was a significant reduction in the concentrations of the two main collagen precursors in the skin after six weeks of either 400 mcg/day (n=9) or 1600 mcg/day (n=10) of inhaled budesonide. Similar collagen changes were found in pre-pubertal children receiving inhaled budesonide in doses ranging from 200-800 mcg/day.[6]

Potential for adrenal suppression may correlate with risk of adverse skin effects

A meta-analysis[3] of 27 studies found that marked adrenal suppression mostly occurred with doses of inhaled corticosteroid above 1500 mcg/day (750 mcg/day for fluticasone propionate). The meta-analysis showed fluticasone had a significantly greater effect on adrenal suppression compared to inhaled beclomethasone or budesonide. The potential for corticosteroid-induced adrenal suppression was found to correlate with the likelihood of skin bruising.[3]

Sun exposure can accelerate skin atrophy

The Centre for Adverse Reactions Monitoring (CARM) has received a report suggestive of sun exposure aggravating the skin atrophic effects of inhaled corticosteroids. There is one published case report[7] of the association between topical corticosteroids, sun exposure and skin atrophy. The pathogenesis of skin atrophy from photoaging (i.e. skin changes as a result of sun exposure) is similar to that of corticosteroids, namely through changes in collagen synthesis.[8-10] It is likely that the effects of sun and inhaled corticosteroids are at least cumulative, if not synergistic.

The potential for skin atrophy can be minimised

The risk of systemic side effects, including skin atrophy, with inhaled corticosteroids can be minimised by using the lowest possible maintenance dose that provides best asthma control. Reviewing the patient's inhalation technique may also be useful. Be aware of other dose formulations of corticosteroids (i.e. intra-nasal, topical and systemic steroids), which should also be kept to a minimum due to the potential for cumulative effects.[11]

There is some evidence that sun exposure can accelerate steroid-induced skin atrophy, the development of which can be limited by protecting the skin, particularly the face and arms, from the sun. Daily use of a broad-spectrum sunscreen (UVB and UVA block) and appropriate protective clothing is recommended.[10,12-14] Patients on corticosteroids should also be encouraged to regularly use moisturisers on their arms and legs, as these may reduce bruising and tearing of the skin from minor trauma.[11] Evidence suggests that topical tretinoin can increase the epidermal thickness of sun-damaged atrophic skin, but long-term use may be necessary.[14] In dermatological practice, topical retinoids are used to help reverse skin atrophy caused by sun exposure or corticosteroid use.

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Correspondence to Dr Marius Rademaker, Dermatology Department, Waikato, Private Bag 3200, Hamilton. E-mail: Rademakm@waikatodhb.govt.nz

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VISUAL DISTURBANCES WITH COX-2 INHIBITORS

ADR UPDATE

Dr David Coulter, Research Associate Professor; Dr David Clark, Senior Research Fellow, Intensive Medicines Monitoring Programme, New Zealand Pharmacovigilance Centre, Dunedin

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Acute, temporary, and sometimes severe, visual disturbances have been reported with celecoxib and rofecoxib use. The eyesight changes appear to be completely reversible on withdrawal of the COX-2 inhibitor. Similar events have occurred with the non-specific non-steroidal anti-inflammatory agents (NSAIAs). In patients who develop acute visual disturbance while on a COX-2 inhibitor or NSAIA, prompt withdrawal is recommended followed by monitoring for resolution of symptoms.

A range of visual disturbances are described

The Pharmacovigilance Centre in Dunedin has received nine reports of visual changes associated with the use of celecoxib and rofecoxib. Six of the reports were for celecoxib (from a total of 726 reports), and three for rofecoxib (out of 487 reports). Two of the case reports are detailed below, while others have been published elsewhere.[1] In all but one of the visual disturbance cases the duration to onset from first taking the COX-2 inhibitor was within four weeks. The eyesight changes were bilateral in eight of the cases. To date, there have been no reports received for the newer COX-2 inhibitors available, probably because of the early stage of monitoring.

The following adverse reactions were reported: blurred vision, abnormal vision, scintillating scotomata, visual field defect and temporary blindness. The World Health Organisation's (WHO) adverse reactions database contains similar reports for celecoxib and rofecoxib. There is one other published report[2] of visual disturbance with celecoxib; and two reports[3,4] of visual disturbance associated with ibuprofen involving a total of four patients, suggesting that visual changes can also occur with the non-specific non-steroidal anti-inflammatory agents (NSAIAs).

Blurred vision, cataract, conjunctivitis, eye pain and glaucoma are listed as adverse effects in the celecoxib (Celebrex®) data sheet[5]; while blurred vision is included in the rofecoxib (Vioxx®) data sheet.[6]

New Zealand case reports provide further detail

Case 1: A man aged 78 took a first dose of rofecoxib 50mg one night and two doses of 25mg the next day for shoulder pain. The following morning he had reduced vision with blurring. He was seen later that morning by his doctor who found no useful vision in one eye and reduced visual acuity of 6/18 in the other. He took no further rofecoxib. Later the same day he was reviewed by an ophthalmologist and his vision was assessed as having returned to normal. This event was recorded as temporary blindness.

Case 2: A man aged 81 was taking celecoxib 100mg daily following knee replacement surgery for osteoarthritis. Three weeks after commencing celecoxib he developed jellybean-shaped loss of vision centrally in each eye. This occurred every day after his morning dose and lasted for a few hours. The celecoxib was stopped and there was no recurrence of the visual disturbance.

Symptoms resolved on prompt discontinuation

In the eight reports where the outcome is known, the patients recovered quickly on withdrawal of the COX-2 inhibitor. Two had experienced similar problems with non-specific NSAIAs; one with indomethacin and the other agent unknown. However, for the other seven patients the acute to patients the acute visual changes were first-time symptoms. The visual disturbances did not recur during periods of observation of up to seven months following withdrawal. None of the patients were re-exposed to celecoxib or rofecoxib.

A plausible mechanism exists

There is evidence that the cyclo-oxygenase enzymes COX-1 and COX-2 are involved in the regulation of retinal blood flow.[7] Interference with the action of these enzymes by either COX-2 inhibitors or conventional NSAIAs may therefore cause acute, temporary disturbance of vision. The clinical picture seen in the reported cases is consistent with this mechanism, although there may be other possible explanations.

Consider iatrogenic eyesight changes in presenting patients

This case series shows acute, reversible and sometimes severe disturbances of vision in close association with the use of celecoxib and rofecoxib. This signal is strengthened by reports held in the WHO database. Prescribers should be aware of these adverse reactions, which are possible with both COX-2 inhibitors and conventional NSAIAs. If eyesight changes occur, the anti-inflammatory medicine should be immediately withdrawn and the patient assessed for response, in particular, resolution of visual symptoms. For patients in whom a severe visual disturbance has occurred, avoiding future exposure to the causative agent and other NSAIAs is recommended.

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Correspondence to Dr David Coulter, NZ Pharmacovigilance Centre, PO Box 913, Dunedin. E-mail: david.coulter@stonebow.otago.ac.nz

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DIARRHOEA WITH BETA-BLOCKERS – BLAST FROM THE PAST

ADR UPDATE

Dr Natasha Rafter, Public Health Medicine Registrar, Auckland University

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Diarrhoea is a possible, but not dose-related, side effect of beta-blocker therapy. If the diarrhoea is severe or persistent, withdrawal of the beta-blocker is recommended but this must be gradual to avoid harmful cardiovascular sequelae.

Reports of diarrhoea with carvedilol

Carvedilol is a non-cardioselective beta-blocker (blocks both $ß_1$ and $ß_2$ adrenergic receptors) with alpha (α_1) blocking activity.[1] It is indicated for the management of essential hypertension, angina pectoris and as adjunctive therapy in chronic heart failure.[2]

The Centre for Adverse Reactions Monitoring (CARM) has received four reports of diarrhoea with carvedilol (Dilatrend®). In three of the reports, severe diarrhoea developed within a week; and in the fourth case, the diarrhoea was moderate and began during the first month of carvedilol treatment. The doses of carvedilol ranged from 6.25mg to 25mg daily. All the individuals experienced improvement in their symptoms on stopping the medicine. In Australia, eleven cases have been reported to the Adverse Drug Reactions Unit.[3]

All beta-blockers can cause diarrhoea

Diarrhoea is a recognised adverse effect of the beta-blockers as a class,[1] and there are cases documented in the literature.[4] As with the other beta-blockers, the carvedilol data sheet describes gastrointestinal symptoms, such as diarrhoea, nausea and vomiting, as being a common occurence (with a frequency of between 1-10%) and not dose-related.[2]

Discontinue beta-blocker treatment gradually if diarrhoea persists

If the diarrhoea persists or is severe, treatment with beta-blockers may need to be withdrawn and alternative therapy commenced. However, if beta-blockers are stopped abruptly there is a risk of rebound hypertension, angina or myocardial infarction especially in individuals with ischaemic heart disease. Therefore, it is necessary to withdraw the beta-blocker gradually over two weeks while monitoring symptoms and blood pressure.[1,2]

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Correspondence to Dr Natasha Rafter, Auckland Regional Public Health Service, Private Bag 92605, Symonds St, Auckland. E-mail: nrafter@paradise.net.nz

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ANTIRETROVIRAL TREATMENT IN ADULT HIV INFECTION IN NEW ZEALAND

Antiretroviral therapy has progressed rapidly over the past decade and has achieved remarkable reductions in HIV-related mortality in most developed countries with ready access to drugs.

The United States Department of Health and Human Services (DHHS) issues guidance documents for the medical management of HIV infection and other issues surrounding HIV infection. These documents contain technical information useful for health care providers. The guideline documents are periodically reviewed and updated by panels of HIV experts.

The Ministry of Health's AIDS Medical and Technical Advisory Committee (AMTAC) endorses the DHHS's November 10, 2003 publication *Guidelines for the Use of Antitretroviral Agents in HIV-1-Infected Adults and Adolescents* as being the standard of care in relation to treatment of HIV-infected adults and adolescents in New Zealand.

The November 10, 2003 version of the Guidelines reflect the practice of New Zealand clinicians in their approach to treating HIV infection, and are available on the Ministry of Health's web site section for HIV and AIDS information (www.moh.govt.nz/aids). The Guidelines can also be accessed directly at www.aidsinfo.nih.gov/guidelines/archive.asp#50

AMTAC will review and make recommendations on a new edition of the DHHS's Guidelines and information will be placed on the Ministry of Health's web site.

SSRI ANTIDEPRESSANTS IN CHILDREN AND ADOLESCENTS

ADR UPDATE

The following letter was sent by Medsafe to all prescribers and pharmacies on 22 March 2004, and was also published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers.

22nd March 2004

Dear Health Professional,

Re: The use of SSRI antidepressants in children and adolescents

The Medicines Adverse Reactions Committee (MARC) has reviewed the efficacy and safety of SSRI antidepressants* to treat Major Depressive Disorder (MDD) in children under 18 years old, and considers the data to be inconclusive. While the MARC is awaiting further data, the following is advised –

- **Initiating treatment: Pharmacological treatment is second-line therapy in the treatment of MDD in children. For children and adolescents, specialist advice should be sought before prescribing any antidepressant.**
- **Continuing treatment: Children and adolescents who are responding well to SSRI therapy should complete the usual course of treatment. If the response is inadequate, specialist advice should be sought.**
- **Stopping treatment: SSRIs should not be stopped abruptly. Doses should be tapered off gradually, and specialist advice sought about further management.**
- **Monitoring: All patients with depression should be monitored for the emergence or worsening of suicidal thoughts and behaviours. Patients should be encouraged to discuss any concerns with their doctor.**

The Medicines Adverse Reactions Committee (MARC) has considered the safety and efficacy of the Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants* for use in treating major depressive disorder (MDD) in people under 18 years of age. There has been recent concern regarding a possible lack of efficacy and possible increased risk of suicidal ideation and self-harm behaviour, when these medicines are prescribed as therapy for children and adolescents with MDD.

In New Zealand, none of the SSRIs have been approved for use in treating MDD in children or adolescents. Please refer to the Medsafe web site for full prescribing information about these medicines (www.medsafe.govt.nz).

On March 10th 2004, the MARC reviewed reports from the UK Committee on Safety of Medicines (CSM), the American College of Neuropsychopharmacology, US Food and Drug Administration (FDA) advisory committees, and the Royal Australian and New Zealand College of Psychiatrists.

The CSM and FDA evaluations of data from clinical trials in children and adolescents with MDD are in broad agreement. They conclude that there is evidence for efficacy of fluoxetine and possibly citalopram, but not for paroxetine, sertraline, or venlafaxine. The evaluations also conclude that there is evidence for increased suicidal ideation and/or behaviour for citalopram, paroxetine, sertraline, and venlafaxine. The CSM concluded that the risk:benefit ratio was adverse for all SSRIs except fluoxetine, and the FDA issued strong warnings about a possible increased risk of suicidality with these medicines.

* Fluoxetine, Paroxetine, Citalopram, Sertraline (and Venlafaxine, a Selective Serotonin Noradrenaline Reuptake Inhibitor (SNRI) with similar properties to the SSRIs) are the only SSRIs currently marketed in New Zealand.

In the opinion of the MARC, the above studies are small in size and confounded by inconsistencies in how safety and efficacy are defined. It is, therefore, not possible to accurately determine the risk:benefit ratio for SSRIs in child and adolescent MDD without additional information. In order to resolve this issue, the FDA has commissioned a further analysis of the raw data from the reported trials. In the interim, the MARC does not consider it necessary to amend the New Zealand prescribing information.

The MARC notes that tricyclic antidepressants have marginal efficacy and poor safety within this age group,[1] and acknowledges that, with the support of specialist advice, SSRIs may have a role in the management of MDD in children under 18 years of age. The MARC has placed a high priority on reviewing the safety of SSRIs as more data become available.

signed by

Dr Stewart Jessamine

Principal Technical Specialist
Medsafe

For further information see:

- www.mhra.gov.uk/news/2003.htm#ssri (UK summary of SSRI MDD studies)
- www.fda.gov/cder/drug/advisory/mdd.htm (US FDA)
- www.acnp.org (American College of Neuropsychopharmacology report)

Cited reference:

1. Hazell P, O'Connell D, Heathcote D, Henry D. Tricyclic drugs for depression in children and adolescents. *Cochrane Database Systematic Review* 2003; (4):CD002317.

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.

Recent additions

Leflunomide (Arava®) – all adverse reactions

Due to increasing use of this disease-modifying agent in the management of rheumatoid arthritis, and the serious nature of some adverse reactions reported both locally and internationally, the MARC requests that prescribers report all adverse reactions associated with leflunomide regardless of severity or seriousness.

Recent deletions

All the following *Adverse Reactions of Current Concern* have been removed (effective from 30 April 2004) as the MARC considers that a good level of awareness by prescribers has been achieved:

- Atypical antipsychotics and hyperglycaemia
- Celecoxib and cardiovascular events
- Diane 35® and 35 ED® and venous thromboembolism
- Estelle 35® and 35 ED® and venous thromboembolism
- Fluticasone (inhaled) and adrenal insufficiency, hypoglycaemia, or seizure
- Hormone replacement therapy and venous thromboembolism
- Rofecoxib and cardiovascular events.

Please report **all cases** of the following adverse reactions to: CARM, 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 (Arava®)	all adverse reactions	See above
SSRI antidepressants	severe agitation, severe restlessness/akathisia, and/or increased suicidality	Vol.23(3), Nov 2002

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

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, New Zealand Ph: (04) 496 2107 Fax: (04) 496 2229 E-mail: sarita_von_afehlt@moh.govt.nz	
Editorial Team:	Dr Stewart Jessamine Dr Karyn Maclennan Dr Jonathan Moy	Principal Technical Specialist Pharmacovigilance Advisor Medical Advisor
Manager, Medsafe:	Clare Van der Lem	
Medsafe web site:	www.medsafe.govt.nz	

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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

H1574

Surname:	First Name(s):	NHI No:
		Ethnicity:
Address:		Date of Birth:
		Sex: M ☐ F ☐

ALL MEDICINES IN USE – ASTERISK SUSPECT MEDICINE(S)

Medicine(s) / Vaccine(s)+ batch no.	Daily Dose	Route	Date Started	Date Stopped	Reason for Use

DESCRIPTION OF ADVERSE REACTION OR EVENT

Date of Onset: ----------

Recovered ☐ Not yet recovered ☐ Unknown ☐ Fatal ☐ Date of Death:

Severe? No ☐ Yes ☐ **Rechallenge?** No ☐ Yes ☐ Result:

OTHER FACTORS

Renal Disease ☐ Hepatic Disease ☐ Allergy ☐ Describe:

OTC Use? ☐ Industrial Chemicals ☐ Other Medical Conditions? ☐ Describe:

REPORTING DOCTOR/PHARMACIST/NURSE

Name:	Telephone:
Address:	Date:
Email address:	

Send completed form to CARM

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

ADVERSE REACTIONS REPORTING GUIDELINES

Please do not hesitate to report ***any suspect reaction of clinical concern***. The following general guidelines apply.

Report adverse reactions to:

- All medicines
- Vaccines
- "Over-the-counter" (OTC) medicines
- Herbal, complementary and alternative remedies.

Report **adverse reactions** and **interactions** that are:

- **serious**
- **adverse reactions of current concern**.[1]

Report **serious allergic reactions** so that a danger or warning can be entered against the patient's name in the national health database.

If in doubt, report.

Reporting may be made on-line, by mail, fax, e-mail or phone

On-line reporting: Register and report on-line at www.otago.ac.nz/carm/report.asp

Reporting form: Use the form overleaf or the card supplied with *New Ethicals Catalogue*. The reporting form can also be downloaded from www.otago.ac.nz/carm/report.asp *or* www.medsafe.govt.nz/profs/adverse.htm

Mail the form to: Freepost 112002
The Medical Assessor
Centre for Adverse Reactions Monitoring
P O Box 913, Dunedin

Or fax it to: (03) 479 7150

Phone: (03) 479 7247

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

Web site: www.otago.ac.nz/carm

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