ISSN 1172-5648

Prescriber Update

Vol. 24 No. 1
June 2003

A publication of

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

MINISTRY OF HEALTH
MANATŪ HAUORA

www.medsafe.govt.nz

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

- Data sheets
- Prescriber Update articles
- Adverse reactions reporting forms
- Consumer Medicine Information (CMI)

www.medsafe.govt.nz

FROM THE EDITOR

On-line reporting of adverse events

It is now possible to lodge adverse reaction reports directly on the web site of the Centre for Adverse Reactions Monitoring (CARM). CARM values your contribution to adverse reaction monitoring in New Zealand, so has introduced the on-line option to make it quicker and easier for you to submit adverse event reports. The on-line reporting system utilises encryption technology, enabling confidential patient data to be transmitted securely. To use the system, you first need to register so please take a minute to do this as soon as convenient (go to www.otago.ac.nz/carm/report.asp). Please note that you will be asked to provide your professional registration number. Once you have registered, you will be able to transmit your adverse event reports to CARM electronically. Give it a try. Of course, you can also use the mail, fax, e-mail or telephone modes of reporting to CARM.

Calling for all brand-switch adverse events

Adverse events have been observed in some patients when switching from one particular 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 encourages prescribers to report adverse events arising from brand-switching so that patterns and trends can be identified, and brands of the medicines investigated if necessary.

Reports of adverse events occurring following change to another brand have recently been received by CARM for these medicines:

- Estelle®
- felodipine
- fluoxetine
- methylphenidate
- paracetamol
- simvastatin.

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

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. It is our editorial policy to ensure that articles dispm/ying 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 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.

Free resources available

- Consumer Medicine Information (**CMI**) poster
- **Prescribing Medicines in Pregnancy** – categorisation of risk of medicine use in pregnancy – booklet (4th edition)
- Medsafe patient information leaflet on **oral contraceptives and blood clots** (March 2002 update).

To order copies of any of these resources, contact Wickliffe: phone 04 496 2277, fax 03 479 0979, email pubs@moh.govt.nz or post an order to the Ministry of Health, c/- Wickliffe Ltd. PO Box 932, Dunedin.

COX-2 INHIBITORS AND HEPATOTOXICITY

IMMP INTENSIVE MEDICINES MONITORING PROGRAMME

Dr David Coulter, IMMP Director, New Zealand Pharmacovigilance Centre, Dunedin

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in May 2003.

As with the non-specific non-steroidal anti-inflammatory agents, liver toxicity may occur with the cyclo-oxygenase-2 (COX-2) specific inhibitors, celecoxib and rofecoxib. They may cause cholestatic, hepatocellular or mixed liver injury; all of which can be severe. Practitioners should be alert to this possibility, particularly as the onset may be rapid.

Some case reports support causal association

As part of the Intensive Medicines Monitoring Programme (IMMP) monitoring of COX-2 inhibitors, 17 reports of hepatotoxicity have been received. Most had an onset time of less than three months. There are three case reports of significant liver injury occurring in association with rofecoxib.

1. A woman aged 85 was being treated with rofecoxib 6.25mg daily for three weeks for inflammatory arthritis. Peak enzyme values were ALP 239, ALT 1409 and AST 1545 units per litre indicating hepatocellular liver injury. The total bilirubin rose to 43 µmol per litre. No other medicines were listed. The liver function test (LFT) results had been normal prior to taking regular rofecoxib and returned to normal after it was withdrawn.
2. A man aged 81 with controlled congestive heart failure and maturity onset diabetes was prescribed rofecoxib (dose not stated) for a sore neck. He became unwell 'almost immediately' and seven days later was admitted to hospital with hepatocellular liver injury. His LFT results were ALP 115, ALT 1111 and bilirubin normal. The only new medicine prescribed was rofecoxib. There was no evidence of viral hepatitis. Two weeks after withdrawal of rofecoxib the ALT level had returned to near normal without change in his other medicines.
3. A man aged 61 was prescribed rofecoxib (dose not stated) for foot pain. After about three months he developed severe cholestatic hepatitis, which was confirmed on liver biopsy. His total bilirubin peaked at 501 µmol/litre. At the same time he developed acute renal failure. He was taking no other medicines. Recovery was complete two months after withdrawal of rofecoxib.

Other case reports included other known hepatotoxic medicines

While the clinical details concerning the above case reports were not complete and the investigations reported were not exhaustive, it is probable that these hepatic events were related to rofecoxib. There were three other reports of similar severity involving celecoxib where the relationship was less clear due to concomitant hepatotoxic medicines including methotrexate and leflunomide.

In addition, there have been eight reports of mild liver function abnormalities with celecoxib and three with rofecoxib. Two of these patients recovered following withdrawal of the COX-2 inhibitor, but the outcome of the others is unknown.

Hepatotoxicity has been reported infrequently in the literature

A literature search revealed a small number of reports of hepatic reactions to celecoxib[1-5] and one with rofecoxib.[6] One patient had an allergy to sulphonamides, and this may have been the risk factor that precipitated her cholestatic hepatitis because celecoxib has a sulphonamide moiety.[2] The New Zealand data sheet for Celebrex® (celecoxib) refers to borderline elevations of LFTs in clinical trials and notable elevations of ALT and AST occurring with no greater frequency than placebo.[7] The Vioxx® (rofecoxib) data sheet states that hepatic failure, hepatitis and jaundice have been reported, but with no comment about causality.[8]

Awareness and early recognition improves prognosis

Hepatotoxicity is known to occur infrequently with the non-specific non-steroidal anti-inflammatory agents (NSAIAs). The IMMP reports of hepatotoxicity with COX-2 inhibitors suggest that this type of reaction is an uncommon class effect of all NSAIAs, both COX-2 specific and non-specific. Patients using COX-2 inhibitors who have symptoms or signs suggestive of liver dysfunction (including an abnormal liver test result) should have the COX-2 inhibitor discontinued.

Competing interests (author): Unconditional programme grants have been received from various pharmaceutical companies, including Merck Research Laboratories USA.

Correspondence to Dr David Coulter, New Zealand Pharmacovigilance Centre, PO Box 913, Dunedin.

References

1. Carrillo-Jimenez R, Nurnberger M. Celecoxib-induced acute pancreatitis and hepatitis: A case report. *Arch Intern Med* 2000;160:553-554.
2. Galan MV, Gordon SC, Silverman AL. Celecoxib-induced cholestatic hepatitis [letter]. *Ann Intern Med* 2001;134:254.
3. O'Beirne JP, Cairns SR. Cholestatic hepatitis in association with celecoxib. *BMJ* 2001;323:23.
4. Nachimuthu S, Volfinzon L, Gopal L. Acute hepatocellular and cholestatic injury in a patient taking celecoxib. *Postgrad Med J* 2001;77:548-550.
5. Alegria P, Lebre L, Chagas C. Celecoxib-induced cholestatic hepatotoxicity in a patient with cirrhosis [letter]. *Ann Intern Med* 2002; 137:E-75.
6. Huster D, Schubert C, Berr F, et al. Rofecoxib-induced cholestatic hepatitis: treatment with molecular adsorbent recycling system (MARS) [letter]. *J Hepatol* 2002;37:413-414.
7. Pharmacia. *Celebrex Data Sheet* 12 March 2002. www.medsafe.govt.nz/profs/Datasheet/c/Celebrexcap.htm
8. Merck Sharp & Dohme (New Zealand) Limited. *Vioxx Data Sheet* 3 October 2002. www.medsafe.govt.nz/profs/Datasheet/v/Vioxxtab.htm

ATYPICAL ANTIPSYCHOTICS MAY CAUSE HYPERTENSION

IMMP
INTENSIVE MEDICINES MONITORING PROGRAMME

Dr David Coulter, IMMP Director, NZ Pharmacovigilance Centre, Dunedin

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in May 2003.

Acute hypertension may occur soon after the commencement of atypical antipsychotic treatment and can be severe, with collapse and altered consciousness. There may be an increased risk if selective serotonin reuptake inhibitors (SSRIs) are administered concomitantly. This adverse reaction appears to be dose-related and it is recommended that blood pressure be monitored during the early stages of atypical antipsychotic therapy, particularly in the presence of SSRIs.

Adverse reaction identified through IMMP monitoring

All of the atypical antipsychotics currently available in New Zealand (i.e. clozapine, olanzapine, quetiapine and risperidone) are monitored in the Intensive Medicines Monitoring Programme (IMMP). From the 572 case reports analysed, hypertension has been identified as a possible adverse reaction. Routine screening of the data revealed this unexpected association.

Hypotension with atypical antipsychotics is a known effect and for all four medicines a total of 19 reports of hypotension, or symptoms suggesting hypotension (e.g. faintness) have been received. In comparison, 13 reports of hypertension have been received; 10 with clozapine, two with risperidone and one with quetiapine. At this stage of monitoring more data have been collected for clozapine and so the actual numbers of reports of hypertension are not a guide to comparative risk. The two most severe cases occurred with risperidone and these are described below.

Case 1

A woman aged 53 had been on risperidone 1mg daily for three days when she collapsed with diminished consciousness (unresponsive to voice) and was found to have a blood pressure (BP) of 190/110 and a tachycardia of 140. The risperidone was withdrawn and by the following day she had recovered. The patient had a history of hypertension and was on treatment with enalapril 2.5mg daily, but the BP had been "normal" prior to taking risperidone. She was also taking paroxetine 40mg and thioridazine 25mg daily.

Case 2

A woman aged 54 was commenced on risperidone 0.5mg daily and after the third dose developed rigidity and a BP of 210/110. Her level of consciousness was reduced. There was no fever, and her creatine kinase and renal function test results were normal. Risperidone was withdrawn and the symptoms resolved within six hours of admission to hospital. She advised that her usual BP was around 145/100 and she was on treatment with cilazapril 5mg daily for hypertension. Other medicines were paroxetine 30mg daily and pantoprazole 40mg daily.

Other cases had similar features

In the other 11 cases of hypertension occurring during atypical antipsychotic treatment, the ages ranged from 15 to 66 years, with eight patients being under 35 years of age. There was a marked rise in BP in each case with the systolic ranging from 140 to 170 and diastolic pressures ranging from 95 to 120. In all but one case, the elevated BP was noted within a month of atypical antipsychotic treatment commencing. Concomitant medicines were recorded for five patients, two of whom were taking the selective serotonin reuptake inhibitors (SSRIs), fluoxetine and citalopram. In three patients the antipsychotic was withdrawn and recovery was rapid, and in two the BP returned to normal with dose reduction.

It seems likely that the hypertensive reaction to atypical antipsychotics is dose-related because it was noted that the BP rose during upward titration of the dose in several patients and two patients recovered with dose reduction. Hypertension

resolved in one patient while continuing on treatment, and in two others the BP was controlled with ACE inhibitors while continuing on the atypical antipsychotic. The outcome is unknown for three patients.

Concomitant use of SSRIs may increase risk of hypertension

Of note is that four of the 13 patients were also taking SSRIs, including the two patients with the most severe hypertension, both of whom were taking paroxetine. The atypical antipsychotics and the SSRIs share some common CYP450 enzymes in their metabolism and there is potential for an increase in blood levels of the antipsychotic through competitive inhibition.

Monitor BP when commencing atypical antipsychotics or adding in SSRIs

The evidence from these case reports is sufficient to establish a signal of a reaction that seems little known. Only a few case reports in the literature describe hypertension, all with clozapine.[1-3] The hypertensive reaction to the atypical antipsychotics is generally of early onset and may be more likely to occur with the concomitant administration of SSRIs. At this stage, it is unclear whether pre-existing hypertension is a risk factor. It would seem prudent to monitor blood pressure during early stages of therapy with atypical antipsychotics, particularly when SSRIs are prescribed concomitantly.

Competing interests (author): Novartis has provided research grants for the IMMP. Novartis is the sponsor of Clozaril® (clozapine).

Correspondence to Dr David Coulter, NZ Pharmacovigilance Centre, PO Box 913, Dunedin.

References

1. Gupta S. Paradoxical hypertension associated with clozapine. *Am J Psychiatry* 1994;151:148.
2. George TP, Winther LC. Hypertension associated with clozapine. *Am J Psychiatry* 1996;153:1368-1369.
3. Ennis LM, Parker RM. Paradoxical hypertension associated with clozapine. *Med J Aust* 1997;166:278.

HELPING MEDICINE CAPSULES GO DOWN

Dr A.D (Sandy) Macleod, Medical Director, Nurse Maude Hospice, Christchurch; Jane Vella-Brincat, Drug Utilisation Review Pharmacist, Clinical Pharmacology Department, Christchurch Hospital

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in May 2003.

The physical properties of capsules predispose them to floating in the mouth when taken with water. As a result, the swallowing of capsules can be problematic. In patients who experience such difficulty, it is suggested that they try leaning forward when swallowing, as this has been found to assist. It may be necessary to reassure patients about this technique as they may initially find it unnatural to execute.

Capsules can be more difficult to swallow than tablets

Many patients have difficulties, both psychologically and physically, swallowing medicines. This may result in poor compliance, treatment failure and decreased quality of life. The swallowing of capsules can be particularly difficult. This is because capsules are lighter than water and float due to air trapped inside the gelatine shell.

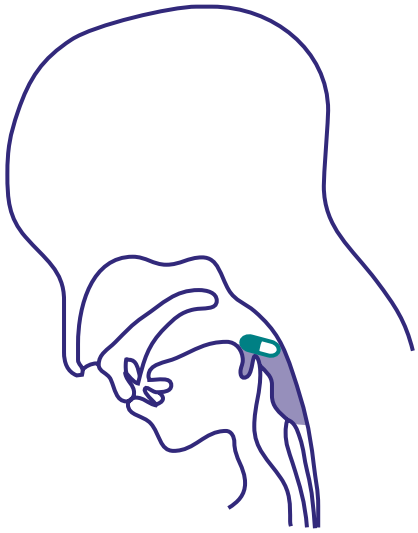
In comparison, tablets are heavier than water and do not float. The usual method of swallowing oral solid dose forms – placing on the tongue, filling the mouth with water, tilting the head back and swallowing – works well for tablets because they do not float and gravity, when the head is tilted back, assists swallowing. If this technique is used with a capsule, it will float on the water in the front of the mouth, placing it in the anatomically incorrect location for ease of swallowing (see figure 1).[1]

Leaning forward may assist

Instead a 'lean-forward' technique has been suggested,[1,2] in which the capsule floats to the back of the mouth and into a good position to be swallowed easily (see figure 2).

Figure 1 – Head tilted back

Figure 2 – Head lent forward



Figures adapted from Kahn[2]

Brown[1] in 1982 noted that this 'lean-forward' technique was "almost universally unknown" amongst physicians, nurses and pharmacists. This was borne out in a recent New Zealand study[3] of healthcare worker volunteers, where very few of the volunteers were aware of this alternative technique to assist swallowing. In this study[3] nine found it easier to swallow a capsule with their head tilted back while 21 found it easier with their head leaning forward. This represented a statistically significant difference, with the 'lean-forward' technique making the swallowing of capsules easier.[3]

Practice may be required to reinforce technique

Although rated as easier by many of these volunteers, the 'lean-forward' technique was also noted to be "awkward" and "unnatural". This is not surprising as swallowing is habitually associated with tilting the head backwards. Patients require instruction, and ideally practice, to grasp this alternative technique. This is particularly so for the elderly, the young, the cognitively compromised and the sick. Once learnt, the benefit rapidly reinforces the practice. This technique does not work for all but may be a viable option for those patients in whom the swallowing of capsules is a problem. It should, however, not be applied to any other oral dosage formulation.

Most capsules are intended to be swallowed whole so patients should be encouraged to trial the 'lean-forward' technique. If swallowing difficulties remain other options, such as a liquid or tablet form of the medicine, can be considered.

Competing interests (authors): none declared.

Correspondence to: Dr A.D (Sandy) Macleod, Medical Director, Nurse Maude Hospice, 35 Mansfield Avenue, Christchurch. Phone (03) 355 0074, fax (03) 355 0067, e-mail sandym@nursemaude.org.nz

References

1. Brown J A. Swallowing medication [letter]. *JAMA* 1982;248(15):1833-1834.
2. Kahn G. Capsule swallowing: The lean-forward technique. *CUTIS* 1985;36(2):144.
3. Macleod A D, Vella-Brincat J, Frampton C. Swallowing capsules [letter]. *Palliative Medicine* (submitted).

UNAPPROVED USE OF MEDICINES

This article has been reprinted from the April 1998 (No. 16) issue of *Prescriber Update*, and the Medsafe web site. There have been no substantial amendments to either the Medicines Act 1981 or the *Code of Health and Disability Services Consumers' Rights* since this time, therefore this article is still relevant.

The Medicines Act 1981 permits a registered medical practitioner, dentist and midwife to prescribe, administer or arrange for the administration of medicines for the treatment of a patient in his or her care. The medicine and its use may or may not be approved. The Act also permits the sale or supply of unapproved medicines to registered medical practitioners, but requires the supplier to notify the Director-General of Health. Approval is obtained when a sponsor company has sought and received Ministerial consent to the marketing of that medicine, and the indications and contraindications etc are set out in the current data sheet.

The *Code of Health and Disability Services Consumers' Rights* places obligations on the provider of services. The consumer has the right to treatment of an appropriate ethical and professional standard, and the provider has the responsibility to ensure treatment, whether approved or unapproved, meets this standard. The consumer also has the right to be fully informed. If the use of a medicine is unapproved, the consumer should be so advised and the provider should be frank about the standard of support for the use and any safety concerns. The Code requires written consent for experimental use of a medicine. The unapproved use of a medicine would be considered to be experimental if there is little or equivocal documented support for the use.

Medsafe is aware that some medical practitioners are confused about their rights and responsibilities with respect to prescribing unapproved medicines, or approved medicines for unapproved uses (such as unapproved indication, dosage or route of administration). Recent correspondence has raised concerns about the legal position of the practitioner who prescribes a medicine in a situation in which it is contraindicated, or against which there are warnings in the data sheet. Examples of these situations are the use of Depo-Medrol injection for epidural administration, and nifedipine capsules in the treatment of hypertensive crisis in pregnancy.

This article will attempt to clarify the situation with regard to the Medicines Act 1981. It will also apply the requirements of the *Code of Health and Disability Services Consumers' Rights* to the unapproved use of medicines. On the Medsafe web site (www.medsafe.govt.nz/Profs/RIss/unapp.htm), there are scenarios illustrating the points made. The reader may find the material more accessible if the scenarios are read first.

Use of medicines regulated by the Medicines Act

The Medicines Act 1981 regulates the use of medicines in New Zealand. It requires that in order for a medicine to be marketed an application with supporting documentation must be made for the consent of the Minister. The Minister's consent is notified in the *New Zealand Gazette*, at which time the medicine, along with a set of indications, dosage instructions and route(s) of administration, is regarded as being approved. Proposed changes, including new indications and changes to the data sheet, also have to be applied for.

Because of this requirement for seeking and obtaining consent, it follows that there will be medicines that may be effective and safe, and approved in other countries, but do not have approval in New Zealand. There will also be other medicines that have been approved with a particular set of indications, but for which there are other recognised indications not applied for in New Zealand. Some unapproved medicines may be used for rare diseases, for which there are few or no treatments approved in this country.

Hence, the need to provide for access to unapproved medicines was recognised when the Medicines Act was formulated. Section 25 of the Act permits registered medical practitioners, dentists and midwives (hereafter referred to collectively as "practitioners") to procure, administer and arrange the administration of an

unapproved medicine. Section 29 permits an authorised supplier or a medical practitioner to supply or sell an unapproved medicine to a medical practitioner provided the Director-General of Health is notified. Both sections of the Act need further explanation.

Section 25 of the Medicines Act permits use of unapproved medicines

The terms of section 25 are inclusive and permissive, allowing the practitioner to "procure the sale or supply of any medicine" for a particular patient in his or her care. "Any medicine" includes approved and unapproved medicines. For dentists "any medicine" applies only to medicines for dental treatment, and for midwives it applies only to medicines for antenatal, intrapartum and postnatal care (Regulation 39, Medicines Regulations 1984).

"Procure the sale or supply" refers to obtaining the medicine through the usual channels such as a pharmacy or a pharmaceutical company, and it also permits the practitioner to use other means of obtaining a medicine such as importation. However, section 25 does not envisage bulk purchase by the practitioner. The use is to be for the treatment of a particular patient under the care of that or another practitioner.

It is worth mentioning, at this point, the use of approved medicines for unapproved uses. Section 25 permits a practitioner to use any medicine (approved or unapproved) for the treatment of a particular patient in his or her care. The Act puts no restriction on the use of a medicine, even in a situation in which it is contraindicated. However, whether the practitioner uses approved or unapproved medicines, he or she must provide care of an adequate professional and ethical standard (see the discussion of the *Code of Health and Disability Consumers' Rights* later in this article).

Section 29 requires notification of sale or supply of unapproved medicines

Section 29 of the Act permits the sale or supply to medical practitioners of medicines that have not been approved, and requires the "person" who sells or supplies the medicine to notify the Director-General of Health of that sale or supply in writing naming the medical practitioner and the patient, describing the medicine and the date and place of sale or supply.

No notification is required for an unapproved use of an approved medicine, nor is notification required if a practitioner imports a medicine to treat his or her patient. However, if an unapproved medicine is sold or supplied to a medical practitioner, that sale or supply should be notified. If the supply is from one medical practitioner to another, the supplying medical practitioner is encouraged to notify the supply, but notification of supply is not mandatory in this case.

It should be noted that section 29 specifies only medical practitioners. This means that if dentists and midwives wish to procure unapproved medicines their sources are limited to other practitioners or to direct importation.

On occasions a pharmacist working in a pharmacy may be involved in the supply of an unapproved medicine as the medical practitioner's agent. If the pharmacy has imported the medicine, it is the pharmacist's responsibility to ensure that the details of supply are sent to Medsafe. If the medicine has been obtained from a distributor for an identified patient then that distributor should be given sufficient information to enable them to report the supply to Medsafe.

Anyone who imports an unapproved medicine for supply to a doctor under Section 29 (other than a hospital or pharmacy) should ensure that they hold a licence to sell medicines by wholesale. They should also ensure that they hold the product specifications and certificates of analysis for each batch imported as required by Section 42.

Patient should be advised of the forwarding of information under section 29

Note that under the Health Information Privacy Code, Rule 3, the medical practitioner must advise the patient that the information about supply of the medicine will be forwarded to Medsafe and recorded on a database as a requirement of the Medicines Act. The keeping of the database enables Medsafe to contact the prescriber if a problem subsequently arises with the medicine, which may require follow-up with the patient.

Consumers' rights spelt out in the Code

The *Code of Health and Disability Services Consumers' Rights*, which was introduced in July 1996, specifies certain rights of consumers of health and disability services and as a result places obligations on the practitioner. The Code covers the right to treatment of an appropriate ethical and professional standard, the right to be fully informed about condition and treatment options, and the right to make an informed choice.

Right to services of an appropriate standard

Right 4 of the Code refers to the right to services of an appropriate standard. This right includes:

2) Every consumer has the right to have services provided that comply with legal, professional, ethical, and other relevant standards.

4) Every consumer has the right to have services provided in a manner that minimises the potential harm to, and optimises the quality of life of, that consumer.

This right covers the professional standard of the service provided. Whether the medicine or use of the medicine is approved or unapproved, the practitioner must approach the decision for its administration in a professional, scientific manner which includes weighing the expected benefits and risks.

This right also applies to the situation where a patient requests the prescription of an unapproved medicine, about which the practitioner knows nothing. In such cases, the practitioner must seek to be adequately informed before assisting the patient to obtain supplies of the medicine. Only then will the practitioner be in a position to comply with Rights 6 and 7, which are discussed below.

It is conceivable that the medical practitioner will be unable to find sufficient information to convince him or her of either the efficacy or the safety of a medicine requested by a patient. The decision must then be made whether or not to assist the patient to obtain the medicine and conduct a clinical trial of one patient. In anticipation of such situations the medical practitioner needs to pre-determine what are his or her minimum criteria for regarding a medicine as a treatment option, and also what will be his or her standard of patient monitoring to minimise harm should the decision be to proceed with treatment in situations where documentation is severely limited.

Right to be fully informed

Right 6 of the Code covers the right to be fully informed:

1) Every consumer has the right to the information that a reasonable consumer, in that consumer's circumstances, would expect to receive, including...

b) An explanation of the options available, including an assessment of the expected risks, side effects, benefits, and cost of each option;...

For an unapproved medicine or unapproved use, the consumer should be advised of the unapproved status. The consumer should also be advised of the degree and standard of the support for the use of the medicine, and of any safety concerns, or warnings or contraindications regarding its use in their particular condition. In using the phrase "Right to be **fully** informed", the Code requires frank disclosure of information including information that may dissuade the consumer from agreeing to use of the medicine.

The following are examples of the information that should be conveyed, as appropriate:

- The medicine is widely used for this indication and its use is supported by well conducted clinical trials;
- The medicine is contraindicated for use in this situation;
- This medicine is approved for use in adults but no studies have yet been published on its use in children;
- The medicine is innovative and little is known about its potential adverse effects; and
- The published studies of the use of this medicine for this indication do not provide consistent evidence of its efficacy.

With regard to the first point above, it is worth noting that a medicine only obtains approval if there has been an application, with adequate supporting documentation, from a sponsor company to the Director-General of Health. There may be adequate data supporting the use of a medicine, or supporting a different indication or dosage regimen, but if no company has submitted an application there can be no marketing approval in this country.

The use of medicines in certain groups, such as infants and small children, pregnant women, and

frail or elderly patients can be a dilemma for the practitioner. Usually trials have not been conducted in these groups for a number of reasons including ethical ones. Therefore, the sponsor company is unwilling and unable to recommend such use in its data sheet and this becomes an unapproved indication.

Right to give informed consent

Right 7 refers to the right to make an informed choice and give informed consent:

6) Where informed consent to a health care procedure is required, it must be in writing if...

b) The procedure is experimental;....

The use of an unapproved medicine, or unapproved use of a medicine will not always be experimental, but in some circumstances the requirement to obtain written consent will apply. These would include situations where:

- There is minimal evidence to support this use;
- The evidence of the efficacy or safety of the medicine used in this manner is equivocal; or
- The use is part of a clinical trial.

Prescribers need to take responsibility for thinking through the issues, deciding in each situation whether the use is experimental or not, and taking the necessary action. If the use is not judged to be experimental the consumer still has the right to make an informed choice and give informed consent to the treatment.

Note that the obtaining of written consent does not mean that the requirements of the Code have been complied with. The obtaining of informed consent is a process which involves effective communication, frank information disclosure and freely given consent. It also involves careful investigation of the clinical condition of the patient and maintaining a current knowledge of treatment options.

Visit the Medsafe web site for **scenarios that illustrate** what is permitted under the Medicines Act, and what is required by both the Medicines Act and the *Code of Health and Disability Services Consumers' Rights*: www.medsafe.govt.nz/Profs/RIss/unapp.htm

This article was prepared in consultation with the Health and Disability Commissioner. The reader should note that the Health and Disability Commissioner does not give advance rulings on interpretation and application of the Code, and hence it is not possible to say in advance that a particular practice is or is not in breach of the Code. This provision is to ensure that each complaint is considered impartially and with an open mind.

Disclaimer: Mention of the therapies in this article should not be regarded as implied endorsement on the part of Medsafe.

Medsafe accepts no responsibility or liability in respect of the actions or omissions of any person arising from or as a consequence of any statement in this article.

MICONAZOLE – WARFARIN INTERACTION REMINDER

ADR UPDATE

Medsafe Editorial Team

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in May 2003.

Prescribers and pharmacists are reminded of the potentially severe interaction between miconazole oral gel (Daktarin® oral gel) and warfarin. Clinically significant increases in the international normalised ratio (INR) of patients who have been stabilised on warfarin can occur following concomitant use of miconazole oral gel.

Significant systemic absorption of miconazole oral gel can occur when the oral mucosa is inflamed, or from the bowel after the gel has been swallowed. The interaction with warfarin is probably less likely when miconazole is administered to the skin or vaginally but in Australia there has been one report of an interaction involving topical miconazole cream.[1]

In other reports in Australia, the increase in INR has usually occurred within a week or two of commencing miconazole oral gel. In the 17 patients on warfarin in whom INR values were known, the INR rose to between 7.5 and more than 18. In eight of these cases, patients presented with bruising, haematuria or mucocutaneous bleeding. Most patients required the withdrawal of one or both medicines.[1]

There have been six reports in New Zealand of the warfarin and miconazole oral gel interaction resulting in INR increases. Four patients presented with bleeding symptoms such as haemarthrosis, haematuria, haemoptysis or epistaxis. INR values ranged from 7.5 to 18 and those patients with bleeding symptoms all had an INR in excess of 10.

As miconazole oral gel can be purchased from pharmacists, without a prescription, both pharmacists and prescribers are reminded to inform patients taking warfarin about the potential for miconazole oral gel to interact with warfarin. Patients taking warfarin who are also given miconazole oral gel should be monitored for change in anticoagulant effect and the dose of warfarin adjusted, if necessary.[2] Both the data sheet and Consumer Medicine Information (CMI) for Daktarin oral gel contain warnings about this interaction.

Competing interests (authors): none declared.

References

1. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Miconazole oral gel elevates INR - a reminder. *Aust Adv Drug React Bull* 2002;21(4):14.
2. Janssen-Cilag Pty Ltd. *Daktarin oral gel data sheet* 23 October 2000. www.medsafe.govt.nz/profs/Datasheet/d/daktarinoralgel.htm

CLOZAPINE AND CARDIAC SAFETY: UPDATED ADVICE FOR PRESCRIBERS

Committee on Safety of Medicines, and Medicines Control Agency, United Kingdom

Reprinted from *Current Problems in Pharmacovigilance* 2002;28:8 with permission from the Medicines and Healthcare products Regulatory Agency (previously the Medicines Control Agency), London, United Kingdom.

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in May 2003.

Patients who develop clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine.

Clozapine is an atypical antipsychotic agent contraindicated in patients with severe cardiac disorders. An increased incidence of myocardial disease in clozapine users has been recognised for some years and information for prescribers has been updated accordingly. A recent re-evaluation of serious adverse cardiac events in association with use of clozapine has resulted in a strengthening of these warnings.

Before starting clozapine therapy, patients are required undergo a history and physical examination. Patients with a history of cardiac illness or abnormal cardiac findings on physical examination should be referred to a specialist for other examinations that might include an ECG and echocardiogram. Clozapine should only be initiated if severe heart disease is excluded and the benefits of treatment are considered to clearly outweigh the risks. The prescribing doctor should consider performing a pre-treatment ECG to allow comparisons if symptoms develop later.

Rare cases of myocarditis have been reported, some of which have been fatal. Post-marketing experience suggests that the increased risk of myocarditis occurs most commonly in the first two months of treatment. Very rare cases of cardiomyopathy have also been reported; these cases generally occurred later in treatment and some were fatal. Pericarditis and pericardial effusion have also been associated with clozapine treatment.

Tachycardia is a common side effect of clozapine treatment that occurs in about 25% of users, especially during dose titration in early treatment. However, it is also a key symptom of myocardial disease. It is therefore essential that patients who have *persistent* tachycardia at rest, especially in the first two months of treatment, are closely observed for other signs and symptoms of myocarditis/cardiomyopathy. These include palpitations, arrhythmias, symptoms mimicking myocardial infarction, chest pain and other unexplained symptoms of heart failure.

A minority of clozapine-treated patients experience ECG changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T-waves, which normalise after discontinuation of clozapine. The clinical significance of these changes is unclear. However, such abnormalities have been observed in patients with myocarditis, which should therefore be considered. If clozapine-induced myocarditis or cardiomyopathy is suspected, clozapine treatment should be discontinued promptly and the patient referred urgently to a cardiologist for diagnostic evaluation.

Key information for prescribers

- Patients must have a history and physical examination prior to starting therapy. The treating physician should consider performing a pre-treatment ECG.
- Patients who have *persistent* tachycardia at rest, especially during the first two months of treatment, should be closely observed for other signs or symptoms of myocarditis or cardiomyopathy. These include palpitations, arrhythmias, symptoms mimicking myocardial infarction, chest pain and other unexplained symptoms of heart failure.
- Patients in whom myocarditis or cardiomyopathy is suspected should stop clozapine and undergo urgent diagnostic evaluation by a cardiologist.
- Patients with clozapine-induced myocarditis or cardiomyopathy must not be re-exposed to clozapine.

Copies of this article can be obtained from: www.mca.gov.uk/ourwork/monitorsafequalmed/currentproblems/cpoct2002.pdf

I'VE MISSED A DOSE; WHAT SHOULD I DO?

Andrew Gilbert, Libby Roughead and Lloyd Sansom; Quality Use of Medicines and Pharmacy Research Centre, University of South Australia, Adelaide, Australia

Reprinted from *Australian Prescriber* 2002;25(1):16-18 with permission.

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in May 2003.

More than 80% of patients occasionally miss a dose of their medication. Health practitioners ought to plan with their patients what to do if a dose is missed. Patients believe that this plan should be a required part of the information received when a medication is prescribed and dispensed. Consumer Medicine Information sheets, which are available for most commonly prescribed medications, contain a section on what to do if a dose is missed. The routine use of these sheets or similar advice may help patients to know what to do when they miss a dose.

Introduction

Why don't consumers know what to do when they miss a dose of their medication? As health professionals we know that the vast majority of patients occasionally miss a dose of their medication. This unintentional non-compliance, and request for advice after the event, is very common in practice. In a study of 205 people, 90% rated having information on 'what to do if a dose is missed' as very important or important and only 1.5% did not want information on this topic.[1] A USA study[2] found that less than 50% of patients received this information.

Given our understanding of the difficulties around compliance with medication regimens, it must be our expectation that many patients will miss doses. Informing them about what to do about a missed dose at the time of prescribing, dispensing and administration would seem to be a logical step towards improved compliance.

Pre-emptive advice

Missed doses could be viewed within the framework of patient non-compliance, however the problems which arise often result because health professionals do not give enough information to allow the patient to safely use the medication. Teaching a patient what to do if a dose is missed and providing strategies to minimise the number of missed doses appears a sensible approach.[3] Providing written information, that includes what to do if a dose is missed, improves people's self-administration of medicines, including corrective action when a dose is missed.[4]

In practice, giving information on what to do if a dose is missed should not be too onerous a task for medical practitioners or pharmacists. Most of the commonly prescribed medications in Australia come with, or have available, a Consumer Medicine Information (CMI) sheet.[a] All CMI sheets have a section entitled 'What to do if you miss a dose'. Giving patients a CMI sheet the first time they receive a medication, and using this material in discussion with patients at the time of prescribing and dispensing would prepare them for this eventuality.

Assessing the importance of a missed dose

The severity of the patient's condition, whether clinically significant breakthrough effects are likely to be observed, and the characteristics of the medication should be considered when deciding the most appropriate strategy following a missed dose. Vulnerable patients are easily recognisable in any practice and include those on medications of low therapeutic index,[b] or suffering from conditions which require constant maintenance of therapeutic concentrations (for example epilepsy and thromboembolic diseases requiring anticoagulation). On the other hand, for most people with hypertension or hypercholesterolaemia a single missed dose will be of little consequence.

The patients should be informed at the time of prescribing and dispensing, of strategies to minimise missed doses and to redeem the situation when a dose is missed. Highlighting the strategy

as it appears on the CMI or writing out an action plan as a reminder to the patient may prove very useful.

While a pre-emptive approach is ideal it is recognised that requests for information about missed doses are common. Knowledge of a drug's half-life, a major determinant of the fluctuation in interdose concentrations at steady state, is useful for making recommendations on what to do if a dose is missed. Upon cessation of therapy, it takes four to five half-lives for the drug to be completely eliminated.

In general, medications, or their active metabolites, with a long half-life tend to create less problems when a dose is missed than medications with a short half-life. However, the clinical effect of some drugs is not related to the half-life. This usually occurs when the drug is acting via an irreversible mechanism (for example aspirin's effect on platelets), via an indirect mechanism (for example the effect of warfarin on blood coagulation), when the drug is a pro-drug (in which case it is the half-life of the active species that is important) or when the drug is converted to an active metabolite which has a long half-life.[5]

Missing several consecutive doses raises additional problems. For example, for drugs with long half-lives it can take a significant time to re-establish therapeutic concentrations when regular dosing resumes unless loading doses are given (for example digoxin). Drugs with short half-lives will lose therapeutic effect rapidly. Further, drugs with first-dose effects, for example an ACE inhibitor in combination with diuretics, may also present clinical problems when normal dosing is resumed. Overall, surprisingly few studies have examined the clinical significance of a missed dose.

Missed doses of the oral contraceptive pill have been well studied. Women taking the pill need to be aware of the risk associated with missed doses and of what to do when a dose is missed. Given the complexity of this information, and the risk of an unwanted pregnancy, it is important that any verbal counselling is supported with appropriate written material. Where a CMI sheet is available this can be used during the consultation. If no CMI sheet is available for the prescribed product, written notes based on the recommendations in the Australian Medicines Handbook are useful.[6]

A table providing examples of medications for which missed doses may be clinically important, and information for patients on what to do, can be viewed at www.medsafe.govt.nz/profs/PUarticles/missed.htm

Conclusion

For the vast majority of patients an occasional missed dose will have little impact on the outcome of therapy. Most CMI sheets include statements such as:

- If you forget to take one or more doses: take your next dose at the normal time and in the normal amount. Do not take any more than your doctor prescribed.
- If you miss one dose, skip it and continue with your normal schedule.

Having this knowledge when starting therapy may be a simple way to alleviate much patient anxiety and in some cases avoid unwanted clinical consequences.

[a] In New Zealand, CMI fact sheets are available for some medicines. These CMI can be freely accessed from the Medsafe web site: www.medsafe.govt.nz/cons.htm

[b] The therapeutic index reflects the range of concentrations between the drug concentration which produces toxic effects and the drug concentration required for therapeutic effects. A narrow therapeutic index means only small increases in concentration can cause toxicity and small decreases in concentration can result in loss of efficacy.

Conflict of interest: none declared

References

1. Howard J, Wildman K, Blain J, Wills S, Brown D. The importance of drug information from a patient perspective. *J Soc Admin Pharm* 1999;16:115-26.
2. Lyons RF, Rumore MM, Merola MR. An analysis of drug information desired by the patient. *J Clin Pharm Ther* 1996;21:221-8.
3. Zind R, Furlong C, Stebbins M. Educating patients about missed medication doses. *J Psychosoc Nurs Ment Health Serv* 1992;30:10-4.
4. Paulson PT, Bauch R, Paulson ML, Zilz DA. Medication data sheets - an aid to patient education. *Drug Intell Clin Pharm* 1976;10:448-53.
5. Sansom L, editor. *Australian Pharmaceutical Formulary and Handbook*. 17th ed. Canberra: Pharmaceutical Society of Australia; 2000.
6. *Australian Medicines Handbook* 2000. 2nd ed. Adelaide: Australian Medicines Handbook Pty Ltd.; 2000. p. 17-9.

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.

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.

Recent additions

Adrenal insufficiency, hypoglycaemia, or seizure with inhaled fluticasone (Flixotide®) – new listing as from March 2003

Due to concerns arising from international reports of these adverse reactions occuring in association with inhaled fluticasone, MARC would like to bring them to the attention of New Zealand prescribers with the intention of obtaining a local perspective on an emerging safety issue. Adrenal insufficiency associated with inhaled corticosteroids can occur due to systemic absorption of the corticosteroid and consequent suppression of endogenous glucocorticoids, leaving insufficient adrenal reserve to respond to stress (e.g. infection). Adrenal insufficiency may also result from abrupt discontinuation or non-compliance with treatment, leading to acute steroid deficiency. It may present as hypoglycaemia, abdominal pain, tiredness or vomiting, with or without seizures or coma. Although adrenal insufficiency can occur with any inhaled corticosteroid, it may be more common with fluticasone because of its greater potency.[1]

Recent deletions

In March 2003, the following *adverse reactions of current concern* were **removed** from the list, due to a good level of awareness by prescribers being achieved:

- hepatic reactions with nefazodone
- serious soft-tissue infection with NSAIAs
- venous thromboembolism (VTE) with oral contraceptives
- warfarin interaction with celecoxib or rofecoxib.

Note: VTE with Diane®, Estelle® and HRT are still being monitored.

Nefazodone (Serzone®) and hepatic reactions

This has been an *adverse reaction of current concern* since February 2000. During this period, up until February 2003, CARM has received 14 reports of hepatic reactions including seven cases of hepatocellular liver injury and five of abnormal liver function test results occurring during treatment with nefazodone. Doses ranged from 200mg to 500mg daily (recommended dose range is 300mg to 600mg/day[2]), and onset of the adverse event occurred between nine days and 15 months from when nefazodone therapy was initiated. Of the 14 cases, 11 had an onset time of four months or less. While hepatic reactions with nefazodone are no longer an *adverse reaction of current concern*, nefazodone continues to be monitored in the Intensive Medicines Monitoring Programme. This will enable MARC to maintain a watching brief. At this stage, no additional safety advice is being issued by MARC however, prescribers are reminded that patients should be alerted to signs and symptoms suggestive of liver dysfunction, such as jaundice, dark urine, anorexia, nausea, malaise, gastrointestinal complaints, or abdominal pain and told to report these to their doctor immediately. If signs, symptoms or evidence of hepatocellular injury occur during treatment with nefazodone, it should be withdrawn. These patients should be presumed to be at increased risk of liver injury if nefazodone is reintroduced. Accordingly, such patients should

not be considered for re-treatment with nefazodone. Initiation of treatment with nefazodone is not recommended in patients with active liver disease or elevated baseline serum transaminases.[2]

References

1. Adverse Drug Reactions Advisory Committee (ADRAC). Fluticasone and adrenal crisis. *Aust Adv Drug React Bull* 2003;22(2). www.health.gov.au/tga/adr/aadrb/aadr0304.htm#1
2. Bristol-Myers Squibb (NZ) Limited. *Serzone data sheet* 5 March 2002. www.medsafe.govt.nz/profs/Datasheet/s/Serzonetab.htm

Please report **all cases** of the following adverse reactions (additions are in **bold**) 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
Atypical antipsychotics	hyperglycaemia	Vol.23(1), Apr 2002 & No.18, Jun 1999
Celecoxib	cardiovascular events	Vol.23(1), Apr 2002
Complementary and alternative medicines*	all adverse reactions	Vol.23(2), July 2002 & No.13, Oct 1996
Diane 35® and 35 ED®	venous thromboembolism	Vol.23(1), Apr 2002 No.20, Feb 2001
Estelle 35® and 35 ED®	venous thromboembolism	Vol.23(1), Apr 2002 & No.22, Oct 2001
Fluticasone (inhaled)	**adrenal insufficiency, hypoglycaemia, or seizure**	**This issue (see previous page)**
Hormone replacement therapy	venous thromboembolism	Vol.23(3), Nov 2002 & No.16, Apr 1998
Rofecoxib	cardiovascular events	Vol.23(1), Apr 2002
SSRIs	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.

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 are added to the IMMP so that unknown adverse effects can be identified as soon as possible. Medicines may also be included in the programme if they are similar to other medicines for which safety concerns exist.

The medicines currently being monitored are listed in the following table (latest additions are in **bold**).

What to report

Successful assessment of the significance of events depends on you reporting all events occurring with IMMP medicines, including adverse reactions and random clinical incidents. Please report:

- all new events including common minor ones
- any change in a pre-existing condition
- abnormal changes in laboratory test results
- accidents
- all deaths and causes
- possible interactions.

Where to report

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

Medicines on the IMMP

Medicine	Proprietary name/s	Indications/Action
Celecoxib	Celebrex	COX-2 inhibitor (selective NSAIA)
Clozapine	Clozaril, Clopine	atypical antipsychotic
Entacapone	Comtan	Parkinson's disease – adjunctive treatment only
Etoricoxib*	**Arcoxia**	**COX-2 inhibitor (selective NSAIA)**
Levonorgestrel intrauterine system	Mirena	progestogen-releasing intrauterine system
Montelukast	Singulair	anti-asthmatic / leukotriene inhibitor
Nefazodone	Serzone	antidepressant / 5HT2 blocker
Olanzapine	Zyprexa	atypical antipsychotic
Parecoxib*	**Dynastat**	**COX-2 inhibitor (selective NSAIA)**
Quetiapine	Seroquel	atypical antipsychotic
Risperidone	Risperdal	atypical antipsychotic
Rofecoxib	Vioxx	COX-2 inhibitor (selective NSAIA)
Sibutramine	Reductil	centrally acting anorexiant
Tolcapone	Tasmar	Parkinson's disease – adjunctive treatment only
Zafirlukast	Accolate	anti-asthmatic / leukotriene inhibitor

* Etoricoxib (tablets) and parecoxib (injection) are new COX-2 inhibitors, which have been added to the IMMP due to on-going concerns about COX-2 inhibitors in general.

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 Principal Technical Specialist Dr Karyn Maclennan Advisor (Science)
Manager, Medsafe:	Clare Van der Lem
Medsafe web site:	www.medsafe.govt.nz

Published with the permission
of the Director-General of Health.

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 **all** reactions to **new medicines** and **all** events to **IMMP medicines**.[2]

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 17.
2. The list of medicines in the Intensive Medicines Monitoring Programme (IMMP) is on page 19.