

Prescriber Update

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FROM THE EDITOR

Don't miss out on prescribing information

Prescriber Update contains articles about adverse reactions and prescribing recommendations. It is published and distributed about three times a year, free of charge. If you or your colleagues are not receiving these hard-copy issues of *Prescriber Update* by mail, then forward your name and postal address to the Editor (contact details on page 28). There is no cost for joining the *Prescriber Update* **mailing list** and your details will only be used for this purpose.

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Prescriber Update articles can be freely accessed at any time from the Medsafe **web site**. Go to **www.medsafe.govt.nz/Profs.htm** and click on *Prescriber Update Articles* in the menu displayed on the left. The list of articles is sorted into those published within the last six months, with the rest in alphabetical order by subject matter (usually the medicine). The names of the medicines in the titles have been bolded to assist location of relevant articles. Alternatively you can use the *Search* function (click on the oval icon with the magnifying glass) and enter a keyword to locate the information on the Medsafe web site.

Key to Prescriber Update articles

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



Adverse Drug Reaction Update articles are written in response to adverse reaction reports lodged with the Centre for Adverse Reactions Monitoring (CARM) and 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 MARC in response to medicine safety issues and overseas experiences.

Use data sheets as a current reference source for medicines

Data sheets are comprehensive documents containing scientific evidence regarding the safety and efficacy of a medicine. The content of data sheets is governed by Regulations under the Medicines Act 1981 and a Regulatory Guideline enforced by Medsafe, as part of the approval process for medicines in New Zealand.

Occasionally, Medsafe may request that a pharmaceutical company update a data sheet with new safety information, such as changed indications or dosage, or additional contraindications, warnings or adverse effects.

The Medsafe web site contains the most recent versions of data sheets for over 1700 medicines that have been approved for use in New Zealand. Medsafe encourages prescribers and other health professionals to use these data sheets as a reference source for medicine information. The data sheets contain similar information to that in hard-copy compilations, but the Medsafe web site has the advantage of being continuously updated electronically. Almost every week, new and revised data sheets are published on the Medsafe web site so you can be assured of quick and easy access to the latest information.

Prescribing Medicines in Pregnancy – copies still available

Additional complimentary copies of *Prescribing Medicines in Pregnancy* may be requested from 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.

New colour for the adverse reaction reporting card

The CARM adverse reaction reporting card has changed to a pale yellow colour. It is hoped that a different colour might help to make the cards easier to find. For your convenience, one of these reporting cards is located in the centre of this and future issues of *Prescriber Update*. Prescribers are encouraged to use these cards to report any suspect adverse reaction of clinical concern. The article on page 21 gives further details on adverse reaction reporting.

Important
Please read

BUPROPION (ZYBAN™) FOR SECOND-LINE TREATMENT ONLY



Dr Michael Tatley, Medical Assessor; CARM, PO Box 913, Dunedin

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in September 2001.

The Centre for Adverse Reactions Monitoring (CARM) has recorded 218 reports of adverse reactions to bupropion (Zyban™) since its launch in New Zealand. The nature and number of reactions are of a similar pattern to that reported in Australia and the United Kingdom but on a smaller scale. Hypersensitivity and neuro-psychiatric reactions are most commonly reported. Bupropion is contraindicated in patients with a seizure disorder, and caution is required with other predisposing conditions or interacting medicines - check the data sheet. The Medicines Adverse Reactions Committee advises prescribers that Zyban should only be considered as a second-line intervention and as part of a smoking cessation programme.

Effective in smoking cessation therapy but problems exist

Bupropion (Zyban™), originally developed as an antidepressant, has recently been identified as a beneficial aid in smoking cessation therapy. In mid 2000, it was introduced in New Zealand for this latter indication. The mechanism by which bupropion acts as a smoking cessation aid is unclear, as is the exact mechanism of antidepressant activity.¹ Recent media attention in the United Kingdom (UK) has focussed on reports of convulsions and deaths in patients who have taken bupropion, and questioned its safety profile.

Bupropion lowers seizure threshold so is contraindicated in predisposed patients

Of the 126 cases of convulsions in bupropion users in the UK, half the patients had risk factors for seizures.² In New Zealand, the Centre for Adverse Reactions

Monitoring (CARM) has received two reports of convulsions. No apparent risk factors are known in these two cases and it has been difficult to establish causality due to incomplete information. These reports are a reminder about the potential for bupropion to precipitate seizures in predisposed patients.

Bupropion is contraindicated³ in patients:

- with a seizure disorder (current or previous), CNS tumour, bulimia or anorexia nervosa
- withdrawing from alcohol or benzodiazepines
- concomitantly receiving monoamine oxidase inhibitors (MAOIs).

Bupropion should be used with extreme caution³ in patients:

- with clinical conditions that can lower the seizure threshold, such as alcohol abuse, diabetes treated with insulin or oral hypoglycaemic agents, and a history of head trauma
- taking medicines that can lower the seizure threshold, including antidepressants, antipsychotics, sedating antihistamines and anorectics.

If patients are taking **any** medicines, check for interactions before prescribing bupropion. Details of interactions are in the Zyban data sheet which is on the Medsafe web site: <http://www.medsafe.govt.nz/Profs/Datasheet/z/zybantab.htm>

Insomnia, depression, urticaria and rash are the most commonly reported reactions

As at August 2001, CARM had recorded 218 reports of adverse reactions to bupropion. These were largely neuro-psychiatric and hypersensitivity reactions which, although not always serious, were severe enough for nearly all of these patients to discontinue treatment. Many of the neuro-psychiatric adverse events reported may be symptoms of nicotine withdrawal, making assessment of the reactions difficult. Hypersensitivity reactions accounted for 25% of reactions reported. Mean duration to onset of symptoms was 15 days for hypersensitivity reactions and 11 days for all others.

While reactions are more common at the higher dose of 300mg daily, 15% occurred at the 150mg daily dose including 70% of the reports of depression-type symptoms. Twenty-five reports (11%) were serious and required either treatment for the reaction or hospitalisation. Bupropion was the sole suspected medicine in 150 of the reports. In only one report was there evidence indicating the presence of known risk factors or potential drug interactions, suggesting that New Zealand prescribers are adhering to the prescribing information.

Multiple factors contribute to the high adverse reactions reporting rate

In comparison, the Adverse Drug Reactions Advisory Committee (ADRAC) in Australia⁴ has received 980 reports, and in the UK⁵ the Medicines Control Agency (MCA) has received 5,593 reports. The high numbers of reported reactions may be partly accounted for by the large number of patients using bupropion, as well as media attention and the higher reporting rate often seen for new medicines.

In Australia and the UK, where bupropion is subsidised, user numbers are around 250,000-300,000⁶ and 419,000², respectively. Bupropion is not subsidised in New Zealand and our user population is estimated to be 23,000.⁷ The adverse reactions reporting rate in New Zealand is similar to that of Australia and the UK.

The most common adverse reactions reported to CARM are listed in the table below and involved hypersensitivity/skin (130 reactions), psychiatric changes (154 reactions) and nervous system (67 reactions). A similar pattern of reactions has been reported in Australia⁴ and the UK.⁵

Bupropion reactions reported most frequently in NZ	
Hypersensitivity/Skin	
Urticaria	42
Rash	29
Pruritis	19
Angioedema	8
Other	32
Psychiatric	
Insomnia	35
Depression	28
Anxiety	23
Depersonalisation	12
Other	56
Neurological	
Tremor	22
Headache	21
Ataxia	6
Other	18

No definite link between bupropion and deaths

In the UK, there have been 37 deaths in patients taking bupropion. The contribution of the medicine to these deaths is unknown and many patients had underlying conditions that could provide alternative explanations including nine who were not on bupropion at the time of death.⁵

An ADRAC review⁸ of 15 reported deaths with bupropion in Australia found various causes of death and not a single consistent mode of death. In addition to being smokers, several patients had other existing risk factors for unexpected death such as alcohol abuse, diabetes or cardiomyopathy. In 10 of the 15 deaths, alternative contributing factors were identified that were at least as plausible as bupropion. Of the other five deaths, there was insufficient information to assess causality and in two of these cases further data are being sought.

ADRAC has also observed that smokers are already at increased risk of cardiovascular death and that early symptoms of cardiovascular disease may have prompted smoking cessation therapy with bupropion.⁴ In the single New Zealand report of non-fatal myocardial infarction, it has not yet been established whether there was pre-existing evidence of cardiovascular disease.

Use bupropion only as a second-line intervention

The Medicines Adverse Reactions Committee (MARC) is continuing to closely review the safety of bupropion through the monitoring of CARM reports, as well as the experiences of overseas agencies. At present MARC is satisfied that the risk:benefit ratio of bupropion is favourable when the medicine is used appropriately as outlined in the Zyban data sheet, including observing all contraindications. However, in view of the significant adverse events experienced in otherwise healthy individuals and the serious nature of the international reports, MARC recommends that Zyban should only be considered as a *second-line intervention **after** unsuccessful trials with other smoking cessation treatments including nicotine replacement therapy*. Medsafe is working with the sponsor of Zyban to update the data sheet to reflect this prescribing advice. MARC also advises that bupropion should only be used as part of a comprehensive support programme for smoking cessation. Zyban information for patients is available as a CMI (Consumer Medicine Information) on the Medsafe web site: <http://www.medsafe.govt.nz/Consumers/cmi/z/zyban.htm>

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TRAVELLERS' THROMBOSIS

Medsafe Editorial Team

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in September 2001.

There is increasing suspicion amongst the travelling public and the media of an association between the occurrence of venous thromboembolism (VTE) and air travel. However VTE can occur with other forms of travel and hence the term travellers' thrombosis. Doctors must be aware of the risk factors for travellers' thrombosis, and if appropriate discuss the need for prophylaxis with at-risk patients who are contemplating long-distance travel. The effectiveness of aspirin or low molecular weight heparin as prophylaxis in moderate and high-risk groups is theoretical at this stage. It would be prudent to advise all travellers about lower leg exercises, hydration, and the symptoms of VTE.

The added risk of VTE after long-distance travel is unknown

At least 200 cases of deep vein thrombosis and pulmonary embolism (collectively known as venous thromboembolism, VTE) after travel have been reported in the last decade.¹ The background incidence of deep vein thrombosis (DVT) in the general population is approximately 1-2 per 1000 people per year,^{1,2,3} and increases with age.⁴ In addition, up to 20% of the total population may have some degree of increased clotting tendency²; therefore it follows that some members of the public are at risk of coincidentally developing DVT when, or soon after, travelling. However, several case series¹ and two case-control studies^{5,6} do suggest an association between travel and a greater risk of VTE, although there is one prospective case-control study⁷ that did not show an association. Consequently, there remains the possibility that the association could still be coincidental.

Despite paucity of evidence making it difficult to measure the actual incidence of VTE after air travel, or travel of any type, the added contribution of recent long-distance travel to VTE risk has been estimated as 0 to 0.4 per 1000 people per year.² Using the mid value of 0.2 means that for every one million people taking one long journey in a year, there may be an extra 200 cases due to the risk from travel,² added to a background incidence of 1500 cases of clinically detectable VTE. This risk estimate is likely to be higher for people with risk factors, and lower for those without.

Travellers' thrombosis rather than economy class syndrome

Immobility when seated was first recognised as a risk factor for the development of DVT in air raid shelters during World War II.⁸ Homans in 1954 reported five cases of DVT after prolonged sitting and suggested that “prolonged dependency stasis, a state imposed by airplane flights, automobile trips and even attendance at the theatre is able, unpredictably, to bring on thrombosis in the deep veins of the legs”.⁹

The Select Committee on Science and Technology, House of Lords in the United Kingdom (UK), believes the term ‘economy class syndrome’ is seriously misleading and the term ‘travellers’ thrombosis’ is more appropriate.² Many of the published reports include cases of VTE which have occurred in business or first class, or in travellers using other forms of travel.^{5,10,11}

It is not clear whether there are factors in the environment peculiar to air travel, such as time zone changes, seasonal shifts, air quality and dehydration, which heighten the risk of travellers’ thrombosis over other forms of travel.¹ A study¹² in healthy male volunteers showed that hypobaric hypoxia can activate

coagulation. Clearly the various long-distance travel modalities share some similar environmental factors such as immobility, the sitting position, and possibly alcohol intake and use of sedative medicines. Until more epidemiological evidence is available, travellers should be made aware of the risks of thrombosis associated with travel involving long periods of immobilisation.

Pre-existing risk factors contribute to DVT development and are independent of travel

A review¹ of data from 223 cases of travellers' thrombosis published in 2000 found that most people became symptomatic of VTE within four days (some during the journey itself), although occasionally cases were diagnosed as long as four weeks later. At least one risk factor for VTE was present in 75-80% of cases, however most of the studies did not include thrombophilia screens. In contrast, a case-control study⁵ found that post-travel DVT was more often idiopathic and only 25% of cases were associated with risk factors.

Until more evidence is available on the pathogenesis of travellers' thrombosis and from epidemiological studies, the risk factors for VTE with travel are considered to be the same as those for VTE under other circumstances. The following list is derived from studies of VTE in surgical patients²:

- Increasing age above 40 years
- Pregnancy
- Former or current malignant disease
- Blood disorders leading to increased clotting tendency
- Inherited or acquired impairment of blood clotting mechanisms
- Some types of cardiovascular disease or insufficiency
- Personal or family history of DVT
- Recent major surgery or injury, especially to lower limbs or abdomen
- Oestrogen hormone therapy, including oral contraception
- Immobilisation for a day or longer
- Depletion of body fluids causing increased blood viscosity.

In addition, there may be risks from varicose veins, obesity and current tobacco smoking.^{1,13} The occurrence of VTE may require a combination of these risk factors to be present.^{1,3}

The minimum prophylactic recommendation is adequate hydration and mobilisation

Recommendations for prophylaxis of travellers' thrombosis are theoretically-based rather than supported by epidemiological evidence. However, it is recommended that all travellers carry out frequent lower leg exercises, maintain adequate hydration, minimise alcohol intake and avoid sedative medicines. Table 1 gives further recommendations.

In light of publicity about travellers' thrombosis, many travellers are taking aspirin before and during travel. However the efficacy data for this are not yet available. In addition, the benefit of aspirin in thrombosis prophylaxis needs to be weighed against the risks of its adverse effects such as bleeding.¹⁴

Two recent studies^{15,16} have examined the effectiveness of elastic compression stockings in the prevention of symptomless DVT after long-haul air travel. Scurr et al¹⁵ conducted a randomised controlled trial of travellers aged over 50 years with no history of thromboembolic problems, flying in economy class. The results showed that twelve of the 100 participants not wearing stockings developed symptomless DVT, of whom four required low molecular heparin; whereas no DVTs were detected in the 100 participants wearing the stockings. The LONFLIT Study¹⁶ included a randomised controlled trial exploring the use of stockings versus no stockings in subjects at increased risk of VTE. They also found that stockings significantly reduced the incidence of VTE.

More needs to be known about the true incidence of DVT occurrence after all types of travel and the clinical significance of symptomless DVT. The House of Lords has recommended that the UK Department of Health commission case-control research into travellers' thrombosis and preventative measures that may be taken.² In New Zealand, there is a large prospective cohort study underway (NZATT, New Zealand Air Travellers' Thrombosis study), following 1000 long-distance travellers for VTE incidence. This study includes a nested case-control design to address risk factor analysis.

Table 1: VTE prophylaxis recommendations for travellers^{1,2}

Risk Categories	Risk factors	Prophylaxis
	None	Give travellers the following advice: • frequent lower leg exercises • regular mobilisation if practical • maintain adequate hydration • minimise alcohol intake • avoid sedative medicines.
Low Risk	Age over 40; obesity; active inflammation; polycythaemia; recent minor surgery (within last three days)	As above plus consider the use of support tights/non-elasticated long socks.
Moderate Risk	Varicose veins; heart failure (uncontrolled); recent myocardial infarction; hormone therapy (including oral contraception and HRT); pregnancy/postnatal; lower limb paralysis; recent lower limb trauma (within six weeks); family history of VTE	All the above plus consider low dose aspirin (if no contraindication) +/- graduated compression stockings.
High Risk	Previous VTE; known thrombophilia; recent major surgery (within six weeks); previous cerebrovascular accident; malignancy	Discuss with travellers the possibility of avoiding or delaying travel. Otherwise, as above but consider low weight molecular heparin instead of aspirin.

Consumer information is available

Many airlines are now issuing health information leaflets with tickets, as well as providing health advice and information on their web sites.^{17,18,19} Information about DVT is also provided by in-flight video and audio channels, and in the airlines' magazines.

In addition, medical practitioners should include advice and education about the symptoms of VTE as part of pre-travel guidance about disease conditions that might be encountered while travelling (e.g. gastroenteritis, malaria). Doctors have an important role to play in assessing the need for active prophylaxis and recommending preventative strategies for VTE to patients. Remind patients with known risk factors to check with their doctor prior to embarking on any form of long-distance travel. Patients with other medical conditions²⁰ (e.g. chronic lung disease, diabetes, otitis media) that may be adversely affected by travel should undergo pre-flight assessment of health status and suitability to travel.

Competing interests (authors): none declared.

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GROWTH RETARDATION WITH INHALED AND INTRANASAL CORTICOSTEROIDS



Medsafe Editorial Team

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Recent studies have shown that growth suppression may occur in children after long-term exposure to inhaled and intranasal corticosteroids. The Medicines Adverse Reactions Committee recommends that prescribers consider the risks and benefits of inhaled and intranasal steroids in children, and use the lowest effective dose.

Previously only systemic corticosteroids implicated

It is generally accepted that exposing children to systemic corticosteroids can impair normal growth even with relatively small doses.¹ However, in the past this has not been thought to occur with steroids delivered via the inhaled or intranasal routes.

Studies of growth suppression with inhaled² and intranasal^{3,4} steroids have shown conflicting results. Many of the studies have been hampered by poor design, insufficient follow-up (generally one year or less), poorly standardised measurement techniques and difficulties in predicting adult height.

FDA requires warnings about growth suppression

Nevertheless, in 1998 the United States Food and Drug Administration (FDA) recommended class labelling about growth suppression on all intranasal and inhaled corticosteroid products in the adverse reactions and precautions sections of the data sheets.⁵ This change reflected studies that showed a reduction in growth velocity in spite of the absence of hypothalamic-pituitary axis suppression (usually measured by the short ACTH stimulation test). Advice was given to use the lowest effective dose, consider risk versus benefit, and monitor growth of paediatric patients.

Long-term studies show 1cm growth reduction in first year

Two long-term controlled studies^{6,7} of inhaled budesonide in children with asthma were published in 2000 (treatment durations averaging four and nine years, respectively). Both studies demonstrated a reduction in growth in the inhaled steroid groups of approximately 1cm, predominantly in the first year of treatment. However, as treatment continued, the growth rates approached that of the controls such that children were expected to attain⁶, or attained⁷, their projected or target adult height. Agertoft and Pederson⁷ found that the initial growth retardation was significantly correlated with younger age ($p=0.04$).

Further research is needed to quantify the effects of inhaled/intranasal corticosteroids on growth in children to determine whether some patients are more sensitive to these effects. Additionally, more needs to be known about whether the use of inhaled/intranasal corticosteroids at certain ages has a greater impact on growth retardation.

Consider risk versus benefit and use lowest effective dose

The Medicines Adverse Reactions Committee (MARC) advises prescribers that growth inhibition and other systemic effects⁸ may occur in children treated with these medicines. In addition, be aware of the cumulative effect of co-prescribing various dose forms of corticosteroids (inhaled, intranasal, oral and topical preparations).

The MARC recommends that the risks and benefits be considered before prescribing inhaled or intranasal corticosteroids to children. It is important to use the lowest effective dose but to balance this against adequate management of chronic conditions such as asthma, as poor control of these can themselves cause growth retardation. If despite these measures, growth suppression still occurs then treatment with medicines other than corticosteroids should be considered.

If prescribers wish to monitor growth rate in children (e.g. those on long-term corticosteroid treatment or using several dose forms of corticosteroids), this can be recorded on growth charts. Ask your local paediatrician which charts they use, or obtain them from the internet.⁹ Measurement of growth rate needs to be done at intervals by the same person using the same equipment and technique each time.

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INTERACTION BETWEEN COX-2 INHIBITORS AND WARFARIN



Medsafe Editorial Team

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The selective COX-2 inhibitors, celecoxib (Celebrex™) and rofecoxib (Vioxx™), may interact with warfarin causing an increase in the international normalised ratio (INR) and putting the patient at risk of a haemorrhagic event. If a COX-2 inhibitor is considered necessary for a patient taking warfarin, the INR should be checked a few days after introduction of the COX-2 inhibitor and monitored closely for the first two weeks. If the INR increases, the dose of warfarin should be reduced or the COX-2 inhibitor withdrawn. Monitor the INR with either option.

Reports of COX-2 and warfarin interaction: INR increase, haemorrhage

The New Zealand Centre for Adverse Reactions Monitoring (CARM) has received one report of a possible interaction between celecoxib and warfarin. A 59-year-old man, stabilised on warfarin, developed haematuria after three doses of celecoxib; his international normalised ratio (INR) had risen to 3.1.

Up to the middle of May 2001, the Australian Adverse Drug Reactions Advisory Committee (ADRAC) had received 37 reports of possible interaction between celecoxib and warfarin. Twenty of these reports described an increase in INR and 17 a bleeding event with or without a recorded increase in INR. In two cases the INR was more than 10. In most cases there was evidence of the interaction within two weeks of starting celecoxib. None of the patients died. Most of the patients were more than 60 years old.

The ADRAC database also holds four reports of possible interaction between rofecoxib and warfarin. Two cases were of raised INR and two of bleeding events, including a fatal cerebral haemorrhage.

The mechanism of the interaction is unknown, but it is possible that celecoxib inhibits the metabolism of warfarin by CYP2C9.^{1,2} Less is known about the interaction with rofecoxib.

Check INR a few days after adding celecoxib or rofecoxib

If celecoxib or rofecoxib are considered necessary for a patient taking warfarin, the INR should be checked a few days after introduction of the COX-2 inhibitor and monitored closely for the first two weeks. The INR should be checked again if the dose of either agent is changed. Particular care should be taken if the patient is elderly, and/or is taking multiple medicines or suffers from multiple diseases. If the INR increases, it may be possible to continue the

selective COX-2 inhibitor by reducing the dose of warfarin.^{2,3} Otherwise the COX-2 inhibitor should be discontinued to avoid a haemorrhagic event. The INR should be checked and restabilised following any dose reduction of warfarin or cessation of the COX-2 inhibitor.

The interaction between COX-2 inhibitors and warfarin has now been included in the list of adverse reactions of current concern (see page 26) in order to encourage reporting of these adverse events and to gather more data about them.

Competing interests (authors): none declared.

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TIAPROFENIC ACID-INDUCED CYSTITIS



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Tiaprofenic acid (Surgam™, Surgam SA™) is a non-steroidal anti-inflammatory agent, which can cause cystitis. Recent New Zealand case reports suggest that some clinicians may not be familiar with this adverse effect. In most cases, the cystitis has developed after taking tiaprofenic acid for months or years. Symptoms are frequency of micturition, urgency, dysuria and suprapubic pain, and are often severe. Urine microscopy shows sterile pyuria and haematuria.

Prompt withdrawal of tiaprofenic acid usually results in complete recovery. Failure to withdraw tiaprofenic acid can result in unnecessary surgery, permanent damage to the urinary tract and renal impairment. Advise patients on tiaprofenic acid to report any urinary symptoms, and also regularly enquire about these.

Spontaneous case reports indicate a link between cystitis and tiaprofenic acid

In 2000, the Centre for Adverse Reactions Monitoring (CARM) received two reports of tiaprofenic acid-induced cystitis, bringing the total number to 17. In one patient, recognition of the cause only occurred when her symptoms resolved on withdrawal of tiaprofenic acid prior to cystoscopy. The Medicines Adverse Reactions Committee (MARC) would like to remind prescribers about this debilitating adverse effect, to assist in early recognition and resolution.

Tiaprofenic acid-induced cystitis was first reported in New Zealand in 1991. Two patients developed non-bacterial cystitis while taking tiaprofenic acid. The cystitis resolved when tiaprofenic acid was withdrawn and recurred on re-introduction. This reaction was brought to the attention of prescribers.¹ In subsequent years, similar cases were seen in other countries. Spontaneous adverse reaction reporting has led to the identification and confirmation of this potentially serious medicine-related disorder.

An analysis of the Committee on Safety of Medicines database in the United Kingdom (UK) showed that the reporting rate for cystitis in the UK was 18 cases per million tiaprofenic acid prescriptions compared with 0.05 - 0.2 per million for other NSAIDs.² Cystitis occurs coincidentally, or only extremely rarely, with NSAIDs other than tiaprofenic acid.

Symptoms can be severe and disabling, and may become persistent

Tiaprofenic acid-induced cystitis is characterised by urinary frequency, urgency, dysuria and suprapubic pain. These symptoms are often severe and disabling, and may become persistent if tiaprofenic acid is continued. Sterile pyuria, haematuria and sometimes proteinuria are found on urine examination.

Cystoscopy typically reveals a diffusely inflamed mucosa, and the bladder is often small and contracted. Histological features are mucosal erosion, submucosal oedema and diffuse infiltration of inflammatory cells sometimes extending into the muscle layer. Eosinophils may also be present. The inflammatory changes can result in fibrosis extending into the ureters, leading to obstruction.² Postulated mechanisms for tiaprofenic acid-induced cystitis include a delayed hypersensitivity reaction³, or a direct toxic effect on the urothelium.⁴

Most patients recover on withdrawal of tiaprofenic acid, avoiding unnecessary surgery

In a case series^{3,5-7} published in 1994, most of the 32 patients experienced significant morbidity over several months, illustrating a lack of awareness by clinicians of the association between tiaprofenic acid and cystitis. Twenty-four of the patients fully recovered upon withdrawal of the tiaprofenic acid. Two patients were rechallenged and experienced a rapid recurrence of symptoms lasting several weeks. Four patients underwent cystectomy and urinary diversion into an ileal conduit for presumed intractable interstitial cystitis. One patient developed hydronephrosis and renal impairment due to ureteric obstruction.

Tiaprofenic acid-induced cystitis usually occurs in older patients on long-term treatment

A case-control study⁸ showed age was the only clinical variable that increased the risk of cystitis. There was a three-fold increase in risk for patients aged > 70 years compared with those aged < 55 years. The median duration of tiaprofenic acid use until onset of symptoms was 6.3 months, and the median time interval from onset of symptoms to cessation of tiaprofenic acid was three months. Time to recovery after tiaprofenic acid is withdrawn has ranged from one day to five months.²

Tiaprofenic acid-induced cystitis is still under-recognised

Tiaprofenic acid-induced cystitis is rare and the market share of this NSAIA is small. Recognition of this reaction may be further impeded by a long delay between starting tiaprofenic acid and the onset of symptoms. It is important to advise patients to contact their doctor if any urinary symptoms develop. Tiaprofenic acid should be used with caution in patients with recurrent urinary tract infections, cystitis or urinary symptoms from any cause, since the symptoms of tiaprofenic acid-induced urinary problems may be masked.⁹

Immediate withdrawal of tiaprofenic acid is essential when any urinary symptoms occur. The longer tiaprofenic acid is continued the greater the likelihood of irreversible damage and unnecessary surgery. Patients on long-term treatment with this medicine need to be regularly asked about urinary symptoms.

Competing interests (author): none declared.

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YOUR GUIDE TO ADVERSE REACTION REPORTING

CARM
CENTRE FOR ADVERSE
REACTIONS MONITORING

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in September 2001.

The Centre for Adverse Reactions Monitoring (CARM) in Dunedin is the national repository for adverse reaction reports. New Zealand health professionals can be proud of their high rate of adverse reaction reporting. These reports help to identify local patterns and contribute to international pharmacovigilance. The reports can also result in safety alerts to prescribers, and national database warnings for individual patients. All health professionals are encouraged to continue reporting adverse reactions to CARM. Please provide as much information as possible. Personal patient details supplied to CARM remain confidential. Reporters of adverse reactions will receive supportive feedback from CARM.

Your adverse reaction reports contribute to the world data pool

New Zealand has the highest rate of reporting adverse reactions to medicines in the world, both in terms of reports per 1000 doctors and reports per million population. This does not reflect a bigger problem in New Zealand; rather we are more diligent about reporting these events. However, it is estimated that only 5% of all reactions are reported so there is still room for improvement.

The goal of adverse reaction reporting is to improve the safety of medicine use. The Centre for Adverse Reactions Monitoring (CARM) in Dunedin is contracted by Medsafe to collect voluntary reports of adverse reactions to medicines, vaccines, herbal products, dietary supplements and blood products. The CARM database holds over 48,000 reports from around New Zealand, providing a local pattern of adverse reactions to medicines. These reports also contribute to international knowledge of pharmacovigilance. They are anonymised and pooled with other countries' reports in the World Health Organisation's International Monitoring Centre database in Uppsala, Sweden. Participating monitoring centres can use this database to complement their own reports.

Reports can help identify NZ patterns and potential safety issues

A medical assessor evaluates each report received by CARM to determine whether there is an association between the adverse reaction and a medicine, and the strength of any association. CARM monitors its database for patterns, clusters and unusual events that could have significance for medicine safety and prescribing practices in New Zealand. The database is also used to support enquiries from health professionals regarding the possibility of adverse reactions as the cause of a diagnostic dilemma.

Ultimately patients benefit from improved safety

When a serious adverse reaction is reported, CARM enters a **danger** (where re-administration of the medicine is likely to be life threatening) or **warning** (where re-administration of the medicine is likely to cause a clinically significant reaction) against the patient's name in the National Health Index (NHI) database. Most hospitals access this database when patients seek health care.

The Medicines Adverse Reactions Committee (MARC) meets four times a year to review published material, all fatal reports and selected reports of significant, unusual or serious reactions reported to CARM. The MARC may

recommend that Medsafe alert prescribers to an adverse reaction through an article in *Prescriber Update* or a 'Dear Doctor' letter. The MARC may also recommend that the pharmaceutical company update the data sheet with advice to improve the safe use of a medicine.

Anyone can report adverse reactions to CARM

Reports from health professionals are preferred, in particular from doctors and other prescribers, pharmacists and nurses. Interestingly, 65% of the reports CARM receives are from community doctors (mostly general practitioners) while hospital doctors contribute 17% of the reports. Pharmacists (community and hospital) submit 2.3% of the reports lodged with CARM. Pharmaceutical companies are another source of reports but unlike other countries where the majority of reports originate from industry, in New Zealand they contribute only a small proportion of the total reports CARM receives.

CARM accepts reports from consumers but where possible an attempt is made to involve the patient's practitioner who often may be unaware of the reaction.

CARM sends replies to reporters of adverse reactions. These written responses may include information about causality, similar reactions and prescribing advice to assist with risk:benefit assessment of future treatment for the patient involved.

New yellow reporting form, same information needed

In June 2001, the CARM adverse reaction reporting form changed back to a pale yellow colour. This was partly due to a trainee intern survey at Dunedin Hospital in April 2001 that showed one barrier to reporting was lack of access to the reporting forms. It is hoped that a return to yellow might help to make it easier to find. This new form was included in the June 2001 issue of *Prescriber Update* and is stapled in the centre of this issue too. Please also note that forms can be downloaded from both the CARM and Medsafe web sites (www.otago.ac.nz/carm or www.medsafe.govt.nz), or obtained by phoning CARM on (03) 479 7185 or e-mailing to carmnz@stonebow.otago.ac.nz

Reporting is as easy as 1, 2, 3

Please follow these steps for recording details of adverse events on the reporting form, and then forward it to CARM by post (Freepost 112002, CARM, PO Box 913, Dunedin) or fax (03) 479 7150.

Step 1: The patient

Patient details (name, address, date of birth, sex and ethnicity) are needed in case a danger or warning needs to be entered in the NHI database, as explained above. The patient details are held at CARM and remain totally **confidential**. They are also used to help identify duplicates if a report has already been received from another source. Please provide the NHI number, if known.

Step 2: The medicine(s) including OTC and alternative health products

The name of the medicine (and brand name if available) suspected of causing the reaction and dose is necessary. Ideally list **all** medicines including OTC and herbal or alternative remedies, and asterisk the suspected medicine if known. Also provide dates of starting and stopping the medicines as this information is particularly helpful when assessing causality.

Step 3: The event

It is important to provide the date of onset of the adverse reaction as this is crucial for causality assessment. The more details, the better; list symptoms, signs, laboratory results, past medical history. Also describe what happened later: did the person fully recover after withdrawal of the medicine (dechallenge), did they have a similar reaction if the medicine was used again (rechallenge), and was the event severe or fatal? Give any alternative diagnoses that have been excluded. More evidence will provide the CARM medical assessor with more certainty when deciding whether the medicine caused the adverse reaction.

If in doubt, report!

Please do not hesitate to report any suspected reaction of clinical concern, even if you are unable to supply all the details outlined above. A copy of the patient's discharge letter from the hospital or specialist is always helpful. It is particularly important to report reactions that are serious, unexpected or of clinical concern, or involve new medicines or interactions.

MARC has a list of medicines with adverse reactions of current concern. Health professionals are additionally encouraged to report these reactions to CARM for causality assessment before review by MARC. This list of Adverse Reactions of Current Concern can be found in each issue of *Prescriber Update* (see page 26) and on the Medsafe web site (<http://www.medsafe.govt.nz/Profs/adverse/cc.htm>).

IMMP events too

Any adverse events in patients taking medicines on the Intensive Medicines Monitoring Programme (IMMP) can also be reported on the CARM reporting form. A list of the IMMP medicines can be found in *Prescriber Update* (see page 27), on the CARM and Medsafe websites, and in the *New Ethicals Catalogue* (on page 8).

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**ADVERSE REACTIONS
OF CURRENT CONCERN**

CARM
CENTRE FOR ADVERSE
REACTIONS MONITORING

Please report **all cases** of these adverse reactions, to the Centre for Adverse Reactions Monitoring (CARM), PO Box 913, Dunedin. The reporting form enclosed (stapled in centre) can be used or it can be downloaded from the Medsafe web site: <http://www.medsafe.govt.nz/Profs/adverse.htm>

These reactions have been identified by the Medicines Adverse Reactions Committee (MARC) as being of current concern due to local reports to CARM and in the international literature. The purpose of this list is to increase awareness and encourage reporting so that more data may be gathered and appropriate action taken (see article on page 21 for outcomes of adverse reaction reporting in New Zealand). The current list is over the page (additions are in **bold**):

Recent additions

COX-2 inhibitors (celecoxib, rofecoxib) and warfarin interaction

Celecoxib (Celebrex™) and rofecoxib (Vioxx™) may interact with warfarin to increase the international normalised ratio (INR) and cause serious haemorrhagic events. CARM has received one report of an interaction between celecoxib and warfarin resulting in haematuria, in a patient whose INR had risen to 3.1. Patients taking warfarin who are prescribed celecoxib or rofecoxib should have their INR checked in the first few days and monitored closely in the first two weeks of combined treatment. See article on page 16 for further information.

Estelle-35™ and thromboembolism

Estelle-35™ (cyproterone acetate and ethinyloestradiol) has been added because it is a generic equivalent of Diane-35™ and was recently granted consent for distribution in New Zealand.

Medicine/s	Adverse reactions of current concern	Prescriber Update reference
Celecoxib-warfarin interaction	increase in INR/haemorrhage	This issue (see previous page)
Cisapride	cardiac arrhythmias	No.18, Jun 1999 & No.14, Feb 1997
Clozapine	hyperglycaemia	No.18, Jun 1999
Diane-35™	venous thromboembolism	No.20, Feb 2001
Estelle-35™	venous thromboembolism	This issue (see previous page)
Herbal medicines	all adverse reactions	No.13, Oct 1996
Hormone replacement therapy	venous thromboembolism	No.16, Apr 1998
Nefazodone	hepatic reactions	No.19, Feb 2000
NSAIDs	serious soft-tissue infection	No.20, Feb 2001
Oral contraceptives	venous thromboembolism	No.17, Dec 1998 & No.11, Feb 1996
Rofecoxib-warfarin interaction	increase in INR/haemorrhage	This issue (see previous page)
Ticlopidine	neutropenia and thrombocytopenia	No.17, Dec 1998 & No.14, Feb 1997

**INTENSIVE MEDICINES
MONITORING PROGRAMME**



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.

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 (no changes since the June 2001 issue of *Prescriber Update*):

Medicine	Proprietary name/s	Indications/Action
Celecoxib	Celebrex	COX-2 inhibitor (selective NSAIA)
Clozapine	Clozaril, Clopine, SBPA Clozapine, Zopine	atypical antipsychotic
Copper IUCD (<i>follow-up only</i>)	Multiload Cu 375	intrauterine contraceptive device
Eformoterol (<i>follow-up only</i>)	Foradil, Oxis	potent long-acting β_2 -agonist
Entacapone	Comtan	Parkinson's disease – adjunctive treatment only
Levonorgestrel intrauterine system	Mirena	progestogen-releasing intrauterine system
Montelukast	Singulair	anti-asthmatic/leukotriene inhibitor
Nefazodone	Serzone	antidepressant/5HT2 blocker
Olanzapine	Zyprexa	atypical antipsychotic
Quetiapine	Seroquel	atypical antipsychotic
Risperidone	Risperdal	atypical antipsychotic
Rofecoxib	Vioxx	COX-2 inhibitor (selective NSAIA)
Salmeterol (<i>follow-up only</i>)	Serevent	potent long acting β_2 -agonist
Sibutramine	Reductil	centrally acting anorexiant
Tolcapone	Tasmar	Parkinson's disease – adjunctive treatment only
Zafirlukast	Accolate	anti-asthmatic/leukotriene inhibitor

Please report all cases of adverse events occurring with IMMP medicines to the Centre for Adverse Reactions Monitoring (CARM), PO Box 913, Dunedin. The reporting form enclosed (stapled in centre) can be used or it can be downloaded from the Medsafe web site: <http://www.medsafe.govt.nz/Profs/adverse.htm>

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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, traditional and alternative remedies

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

- **serious**
- **adverse reactions of current concern**¹

Report all adverse 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.

To report: Use the pre-addressed postage paid adverse reactions card supplied
with *Prescriber Update* or *New Ethicals Catalogue*.

Or: The form can be downloaded from www.otago.ac.nz/carm/reporting.html or
www.medsafe.govt.nz/profs/adverse.htm

Mail the form to: Freepost 112002
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Web site: www.otago.ac.nz/carm

1. The list of adverse reactions of current concern is on page 26.

2. The list of medicines in the Intensive Medicines Monitoring Programme (IMMP) is
on page 27.