

# Prescriber Update

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## FROM THE EDITOR

### New-look A4 format

Welcome to this first issue of *Prescriber Update* in the larger A4 format. Increasing the size of *Prescriber Update* has enabled the table of contents to be placed on the front cover so at a glance you can determine which articles are of particular interest. This change, along with more concise articles, will enhance the visual appeal and reduce the number of pages, making *Prescriber Update* more readable for busy health professionals.

### Change to the issue numbering system

Medsafe has introduced a new numbering system for the hard copy issues of *Prescriber Update*, effective immediately. The consecutive numbers will be replaced with volume and issue numbers; this one is volume 23, number 1 (following on from the previous system of which the last issue was No. 22). Sequential page numbering will also be implemented. These changes will align the referencing of *Prescriber Update* to that of other medical journals, and will not be applied retrospectively.

### Get in the know

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 16). There is no cost for joining the *Prescriber Update* mailing list and your details will only be used for this purpose.

### On-line resources

The Medsafe web site ([www.medsafe.govt.nz](http://www.medsafe.govt.nz)) contains the following resources which you can freely access at any time:

- *Prescriber Update* articles
- Data sheets for medicines
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- Adverse reaction reporting form.

### CARM / IMMP fax number is now (03) 479 7150

The Centre for Adverse Reactions Monitoring (CARM) and the Intensive Medicines Monitoring Programme (IMMP) have a new fax number. The CARM / IMMP offices have shifted location and faxes sent to the old number (03 477 0509) are now received only by the Poisons Centre. The new fax number is **(03) 479 7150**. The postal address and phone numbers remain unchanged.

### CME points for IMMP questionnaires

The Royal NZ College of General Practitioners has agreed that CME points may be claimed for completing IMMP questionnaires. Each completed questionnaire will be worth 0.5 CME point and up to 10 points per year may be claimed. It is planned that GPs who qualify will receive an annual statement from the IMMP after the end of each calendar year verifying the total number of points earned. These points can then be claimed by presenting the statement to the College.

### 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 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.

## VENOUS THROMBOEMBOLISM WITH DIANE 35™ AND ESTELLE 35™



*Dr Ruth Savage, Medical Assessor, Centre for Adverse Reactions Monitoring, Dunedin*

This article was distributed to all prescribers, pharmacies and relevant organisations in March 2002, along with a 'Dear Doctor/Midwife/Pharmacist' letter, an updated patient leaflet and Medsafe (Ministry of Health) advice on the prescribing of oral contraceptives. All this material was published on the Medsafe web site in March 2002. Copies can be obtained from [www.medsafe.govt.nz/hot.htm](http://www.medsafe.govt.nz/hot.htm)

**The Medicines Adverse Reactions Committee reminds prescribers to confine the use of Diane 35/35 ED™ and Estelle 35/35 ED™ to women with polycystic ovary syndrome, hirsutism, androgenic alopecia and pronounced acne. A recent case-control study has found a four-fold increase in the risk of venous thromboembolism with oral contraceptives containing cyproterone acetate compared with a second generation oral contraceptive. Similar risk estimates have been found in previous smaller studies. From all these studies, it is concluded that the risk of venous thromboembolism with cyproterone-containing contraceptives is at least as great as with third generation oral contraceptives.**

### Higher risk of VTE with cyproterone-containing OCs vs a second generation OC

A new case-control study of venous thromboembolism (VTE) and combined oral contraceptives (OCs), using the UK General Practice Research Database (GPRD), was published in October 2001.<sup>1</sup> The intention of this study was to assess the risk of VTE in women taking OCs containing cyproterone acetate and ≤ 35 mcg of ethinyloestradiol (CPA/EE) compared with women taking levonorgestrel and ≤ 35 mcg ethinyloestradiol (LN/EE), a second generation OC.

Cohorts of 24,401 women taking CPA/EE and 75,000 women taking LN/EE were identified from the GPRD. Twenty-six women from these cohorts who had a confirmed diagnosis of deep vein thrombosis or pulmonary embolism (PE) were identified as cases. Matched controls were drawn from the same cohorts. The relative risk of VTE for women taking CPA/EE was 3.9 (95% CI 1.1-13.4) compared with those taking LN/EE.<sup>1</sup>

The background incidence of VTE in women aged 15-44 years not using combined OCs is 0.5-1 case per 10,000 woman-years.<sup>2</sup> In users of second

generation OCs, the incidence of VTE has been estimated at about 2 per 10,000 woman-years of use and 3-4 per 10,000 for women taking third generation OCs.<sup>2</sup> Using these figures and the GPRD study,<sup>1</sup> the incidence of VTE for women taking OCs containing cyproterone can be estimated at about 8 per 10,000 woman-years.

### Previous studies support recent findings

Two earlier studies<sup>3,4</sup> raised concerns about the risk of VTE with cyproterone-containing contraceptives. However, the numbers of cases and controls taking CPA/EE in these studies were very small so firm conclusions could not be drawn. The World Health Organisation (WHO) study<sup>3</sup> provided the first evidence of a difference in risk of VTE between second and third generation OCs. Within this study there were nine cases and three controls using CPA/EE. The risk of VTE with this preparation was five times greater than with LN/EE. The table below compares the relative risks of VTE with combined OCs in the WHO<sup>3</sup> and GPRD<sup>1</sup> studies. This table also shows that the increased risk with CPA/EE is similar to that found with third generation OCs (i.e. those containing desogestrel or gestodene).

### Relative risk (odds ratio) of VTE with cyproterone-containing and third generation OCs compared with second generation OCs

Study	OC progestogen (a = 2 <sup>nd</sup> generation; b = 3 <sup>rd</sup> generation)	Adjusted odds ratio	95% CI
WHO <sup>3</sup>	levonorgestrel <sup>a</sup>	1.0	reference group
	desogestrel or gestodene <sup>b</sup>	2.7	1.6 - 4.6
	cyproterone	5.1	1.3 - 20.3
GPRD <sup>1</sup>	levonorgestrel <sup>a</sup>	1.0	reference group
	cyproterone	3.9	1.1 - 13.4

The second investigation<sup>4</sup> was a New Zealand study of fatal PE, which included two case patients who had been exposed to CPA/EE (neither of these deaths was reported to CARM). Despite this small number and a resulting wide confidence interval, the risk estimate of 17.6 (95% CI 2.7-113.0) compared with no OC use was similar to the estimate of 14.9 in the WHO study<sup>3</sup> and 13.3 which can be derived from the GPRD study.<sup>1</sup>

### **CARM has received 15 reports of pulmonary embolism with CPA/EE**

In New Zealand, the brands of cyproterone-containing oral contraceptives currently available are Diane 35/35 ED™ and Estelle 35/35 ED™. Up until January 2001, the Centre for Adverse Reactions Monitoring (CARM) had received 13 reports of VTE occurring in women taking CPA/EE. Ten of these 13 women had developed PE. In February 2001, VTE with Diane 35/35 ED was classified as an *adverse reaction of current concern* (see page 12). From February 2001 until November 2001, CARM received five more reports of PE. None of these 18 cases was fatal. The indications, where known, were contraception in ten patients, acne in five and irregular menstruation in two. Estelle 35/35 ED were added to the list of *adverse reactions of current concern* in October 2001.

### **No evidence that indications for CPA/EE falsely elevate risk estimates**

Obesity is more prevalent in women with androgenic disorders and CPA/EE is indicated in these women. It has been argued that because obesity is associated with an increased risk of VTE, use in these indications would account for the increased risk observed with CPA/EE rather than a true increase in thrombogenicity compared with other OCs. In the GPRD study<sup>1</sup> adjusting the results for a history of hirsutism, acne, polycystic ovary disease and asthma, as well as body mass index and smoking, did not change the risk estimate.

### **Prescribe only to women with androgen-dependent disorders**

The evidence presented indicates that combined OCs containing cyproterone are at least as likely as third generation OCs to cause VTE. The Medicines Adverse Reactions Committee reminds prescribers to confine the prescribing of Diane 35/35 ED and Estelle 35/35 ED to women with

polycystic ovary syndrome, hirsutism, androgenic alopecia and pronounced acne, and as contraception in women with these conditions.<sup>5,6</sup> All patients currently on these medicines should be reviewed for the appropriateness of this therapy. Both new and current patients should be fully advised of the risks of VTE. When prescribing Diane 35/35 ED or Estelle 35/35 ED, observe the contraindications, precautions and risk factors for VTE. Where these medicines are being used for contraception, follow the Ministry of Health advice<sup>7</sup> on the prescribing of combined OCs.

The patient information leaflet on OCs and blood clots has been updated, and can be obtained from the Medsafe web site (<http://www.medsafe.govt.nz/Consumers/leaflets/oralcontraceptives.htm>). Copies are also available free of charge from Wickliffe: phone (04) 496 2277, fax (03) 479 0979, e-mail [pubs@moh.govt.nz](mailto:pubs@moh.govt.nz) or post an order to the Ministry of Health, c/- Wickliffe Ltd, PO Box 932, Dunedin.

Product information in the form of *consumer medicine information* (CMI) is also available for consumers. This can be downloaded from the Medsafe web site (<http://www.medsafe.govt.nz/Consumers/cmi/d/diane35.htm> or <http://www.medsafe.govt.nz/Consumers/cmi/d/diane35ED.htm>).

Competing interests (author): none declared.

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## REASSURING NEWS ON SUSPECTED VACCINE ADVERSE REACTIONS



*Medsafe Editorial Team*

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in March 2002.

**Recent studies have confirmed that there is no association between infant immunisation and sudden infant death syndrome, between MMR vaccine and either autism or bowel disease, and between hepatitis B vaccine and multiple sclerosis.**

The Medicines Adverse Reactions Committee (MARC) has reviewed recent studies of some suspected vaccine adverse reactions. This article reflects the views of the Committee and updates advice in earlier *Prescriber Update* articles.<sup>1-4</sup>

### DTPH AND ORAL POLIO VACCINES AND SIDS

#### **SIDS is associated with illness but not infant immunisation**

Studies,<sup>5</sup> including one<sup>6</sup> conducted in New Zealand, have found no association between sudden infant death syndrome (SIDS) and childhood vaccination. SIDS occurs in infants at the age at which they are receiving their immunisations. Hence, close temporal relationships with vaccination are inevitable in some cases.

A recent case control study conducted in the United Kingdom<sup>7</sup> included a base cohort of 470,000 births and identified 303 deaths attributed to SIDS. The odds ratio for SIDS with vaccination uptake (DTPH and oral polio vaccines) after adjusting for matching and the infants' sleeping environment was 0.67 (95% confidence interval 0.31-1.43). Five percent of SIDS deaths and reference sleeps (the reference sleep for each control infant occurred in the period of the day in which the matched case infant had died) occurred within 48 hours following vaccination. Babies who died of SIDS were more likely to have needed medical attention in the 24 hours before death than their matched controls (21% and 7%, respectively). The results of this study<sup>7</sup> are consistent with there being no association between DTPH and oral polio vaccination and SIDS.

### MMR VACCINE, AUTISM AND BOWEL DISEASE

#### **No association between MMR vaccine and autism**

The assertion that there was an association between MMR vaccine and autism, as a result of bowel abnormalities, was made by Wakefield et al<sup>8</sup> in 1998 on the basis of a case series. However, subsequent evidence has not supported this alleged association.<sup>3,9</sup> Two recent studies have compared the rate of uptake of vaccination with the rate of diagnosis of autism over time using United Kingdom<sup>10</sup> and Californian<sup>11</sup> data. Both studies found steep rises (5- to 7-fold) in the number of cases of autism occurring over periods for which the uptake of MMR vaccine was almost static (about 97%) in one study<sup>10</sup> or increased by a small percentage (10%) in the other.<sup>11</sup> The increase in uptake of MMR vaccine could not account for the rise in diagnosis of autism in either study. A further study<sup>12</sup> found no association between MMR vaccine and a distinct syndrome of autism involving regression or autism coupled with gastrointestinal symptoms. A recent review<sup>13</sup> has summarised the evidence regarding MMR vaccine and autism.

#### **Bowel disease not linked to measles infection or vaccine**

Initial findings of an association between exposure to measles in utero or measles infection in early childhood and inflammatory bowel disease later in life have not been confirmed.<sup>3,14</sup> A recent case control study<sup>15</sup> of 142 persons with inflammatory bowel disease found no association with MMR or other measles-containing vaccine. However, the

authors considered that a small increase in risk would not have been detected in their study. The MARC considers that the overall balance of evidence is not consistent with an association between MMR vaccine and bowel disease.

Recently the American Academy of Pediatrics<sup>16</sup> published its conclusions that the available evidence does not support an association between MMR vaccine, autism and bowel disease. The American Institute of Medicine<sup>17</sup> reached a similar conclusion with regard to autism.

## HEPATITIS B VACCINE AND MULTIPLE SCLEROSIS

### No association between hepatitis B vaccine and multiple sclerosis

Three recent studies have examined the possibility of an association between hepatitis B vaccine and demyelinating disease, specifically multiple sclerosis. One study<sup>18</sup> conducted in adolescents in British Columbia found no difference in incidence of multiple sclerosis before and after initiation of the hepatitis B vaccination programme.

### Hepatitis B vaccine not associated with new onset multiple sclerosis in women

Another study<sup>19</sup> using the cohort of women in the US Nurses' Health Study identified 192 women with multiple sclerosis and matched these to 534 healthy controls. After adjustment for age, the relative risk of multiple sclerosis in women vaccinated with hepatitis B vaccine compared with unvaccinated women was 0.9 (95% CI 0.5-1.6). Restricting the analysis to those vaccinated within two years of the onset of disease did not increase the association.

### Relapse of multiple sclerosis did not follow vaccination

The third study<sup>20</sup> looked for an association between relapse and vaccination with any vaccine in 643 patients diagnosed with multiple sclerosis who had been relapse-free in the 12 months preceding the relapse. In this study exposure to vaccination in the 2-month period immediately preceding the relapse was compared with exposure in the preceding relapse-free 2-month periods. The relative risk for relapse with hepatitis B vaccine was 0.67 (95% CI 0.20-2.17).

None of these studies found evidence for an association between hepatitis B vaccine and multiple sclerosis or relapse of multiple sclerosis.

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## LOW DOSE ORAL STEROIDS CAN INCREASE FRACTURE RISK



*Marius Rademaker, Hon Associate Professor and Specialist Dermatologist, Hamilton and the Medsafe Editorial Team*

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**Corticosteroids can reduce bone density and increase the risk of fractures. This occurs quite quickly and even with low doses. It is estimated that up to 50% of patients using oral corticosteroids will develop bone fractures. Upon cessation of the steroid, fracture risk decreases. Preventative measures include using the lowest possible corticosteroid dose and regularly reviewing the need for continuation. Also address factors such as smoking, calcium intake and abnormal vitamin D levels. Bisphosphonates and sex hormones can be used to treat reduced bone density.**

### **Risk factors include age and concurrent inflammatory disease**

The incidence of fractures in patients taking corticosteroids ranges from 11%<sup>1</sup> to 50%.<sup>2</sup> The risk of developing steroid-induced osteoporosis is increased in persons older than 50 or younger than 15 years of age, those with a slim build and in women who are post-menopausal.<sup>1</sup> Corticosteroid users with medical conditions such as rheumatoid arthritis,<sup>2</sup> chronic obstructive pulmonary disease, amenorrhoea and inflammatory bowel disease are also at increased risk.<sup>3</sup> Bone density during steroid use is related to duration of steroid treatment and average dose, as well as factors that influence pre-treatment bone density such as weight and age.<sup>1</sup>

### **Loss of bone mineral density occurs rapidly but can be reversed**

Bone loss appears to be greatest in the first two to three months of corticosteroid use.<sup>1,4,5</sup> Fracture risk returns to baseline when steroid treatment is discontinued, with the risk reduction occurring mostly within the first year of stopping.<sup>5</sup> As a general guide, the period required for the restoration of bone density is approximately equal to the period of treatment.<sup>6</sup>

### **Even doses as low as 5mg daily can increase bone fracture risk**

While the minimum dose for steroid-induced bone loss is unknown, reduced bone density and fractures have occurred with doses as low as 5mg

of prednisone per day.<sup>1</sup> A study<sup>5</sup> of over 200,000 oral corticosteroid users found that the risk of fracture was augmented with increasing dose. Even at daily doses of prednisone equivalent to 2.5-7.5mg, there was an increased risk of hip and vertebral fractures, compared to the control group on no corticosteroids.<sup>5</sup> It is unknown whether bone density is affected by short, tapered courses of steroids such as those prescribed for asthma exacerbations.<sup>4</sup>

### **Consider prophylaxis to minimise risk of osteoporosis**

Preventative measures may be beneficial and include using the minimum effective corticosteroid dose, and regularly reviewing it.<sup>7</sup> Alternate-day therapy does not reduce the risk of bone loss, but may help minimise hypothalamic-pituitary-adrenal suppression.<sup>8</sup> Where practical, address factors such as high alcohol intake,<sup>3</sup> smoking and low body weight, and prescribe calcium supplements.<sup>9</sup> Also encourage patients to undertake regular weight-bearing exercise.<sup>7</sup> Check serum 25-hydroxyvitamin D levels and normalise with calciferol if necessary.<sup>9</sup> Bone density monitoring is recommended in patients taking corticosteroids long term.<sup>10</sup>

### **Pharmacological intervention includes bisphosphonates and sex hormones**

If bone density is reduced, the first treatment of choice is bisphosphonates such as cyclical

etidronate plus calcium, or alendronate.<sup>9</sup> Hormone replacement therapy (HRT) may also be beneficial in post-menopausal women,<sup>9</sup> however the risks and contraindications of HRT need to be considered. Testosterone therapy may be indicated in men with androgen deficiency.<sup>10</sup> Intervention should also be offered to patients with a past history of fracture after minimal trauma, as this indicates the skeleton is less able to cope with the usual strains of daily living.<sup>10</sup>

Competing interests (authors): none declared.

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## CEREBROVASCULAR EVENTS WITH SUMATRIPTAN



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This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in March 2002.

**Sumatriptan (Imigran™) was monitored in the Intensive Medicines Monitoring Programme for eight years in a cohort of almost 15,000 patients. A number of cerebrovascular events were identified at a rate of 1 per 1,000 patients. The nature of these events highlights the importance of accurate diagnosis in patients with first presentation of migraine in middle age or later, as well as observing age and dose restrictions. Sumatriptan is contraindicated in patients with a history of transient ischaemic attacks or stroke.**

### **Most cerebrovascular events identified for sumatriptan are potentially preventable**

Sumatriptan succinate (Imigran™) is used for the acute treatment of migraine<sup>1,2</sup> and cluster headache.<sup>1</sup> It is administered either subcutaneously or orally at the onset of symptoms, and appears to act mainly by constricting the cranial blood vessels.<sup>1,2</sup> From 1991 to 1999, adverse events associated with the use of sumatriptan were monitored in the Intensive Medicines Monitoring Programme (IMMP) in a cohort of 14,964 patients.

A total of 2,344 reports were received, describing 3,978 adverse events. A review of these data identified a small but significant number of cerebrovascular events, at a rate of 1 per 1,000 patients. There were 15 reports of cerebrovascular events; 13 patients were using the subcutaneous preparation and two taking sumatriptan orally. There was one fatal outcome and other events ranged from severe stroke with permanent disability to temporary dysphasia. Several of these events occurred in patients with known risk factors and therefore were potentially preventable.

### **Before prescribing sumatriptan, consider differential diagnosis, age and pre-existing conditions**

#### **Incorrect diagnosis**

In two patients, conditions other than migraine were causing the headaches, namely parasagittal meningioma and subarachnoid haemorrhage.

They were aged 46 and 78 years, respectively. In both, migraine appeared to be a new diagnosis and sumatriptan was administered for the first time. This highlights the need for a careful differential diagnosis in patients presenting with apparent migraine for the first time in middle age or later.

#### **Age**

Two patients were aged 78 and 85. The data sheet states that 'the use of sumatriptan in patients over 65 years is not recommended'.<sup>1,2</sup> However when the condition is disabling, it may be reasonable to decide to use sumatriptan above the recommended age after careful risk-benefit assessment and with informed consent of the patient.

#### **History of cerebrovascular disorder**

Two patients who experienced cerebrovascular events had a history of transient ischaemic attacks (TIAs). Sumatriptan is contraindicated in patients with a history of stroke or TIA.<sup>1,2</sup>

### **Maximum recommended dose of sumatriptan should not be exceeded**

One patient, who had used subcutaneous sumatriptan for a number of years, suffered a pontine infarct one week after using five doses in four days. After exhaustive investigation, no cause was found, nor were there any risk factors for cerebrovascular disease. A causal association seems unlikely in view of a two-hour plasma half-life for the subcutaneous route. However, the possibility has been raised that multiple doses may cause prolonged binding to cerebral vascular

receptors.<sup>3</sup> This patient used sumatriptan within the recommended guidelines, but an IMMP report has also been received of spasm causing occlusion in a peripheral artery after the recommended dose was exceeded. The maximum dose of sumatriptan in 24 hours is 12mg subcutaneously or 300mg orally.<sup>1,2</sup>

### **It is important to observe contraindications and precautions**

Some of these cerebrovascular events might have been hemiplegic or aphasic migraine. However, the majority of patients were known to have had a long history of migraine without hemiplegia or aphasia occurring. In addition, the cerebrovascular events developed only after the use of sumatriptan, making hemiplegic or aphasic migraine unlikely diagnoses. When the contraindications and precautions for dose, age and pre-existing conditions are observed, sumatriptan is unlikely to increase the risk of cerebrovascular events.

Competing interests (author): A grant to assist monitoring was received from GlaxoWellcome in 1998.

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## TALKING THE TALK

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**A New Zealand survey conducted to determine the level of understanding of some common medicine-related terms found that many people do not know the meaning of words such as hypertension and decongestant. The scope of understanding varied according to ethnic group, gender and education status. Health professionals have an obligation to ensure that consumers understand the information given to them. The results of this survey illustrate how and why misunderstandings can arise in regard to health information. Take this into consideration when communicating with consumers. Use patient-friendly language and check that your patients have understood the information.**

### Low level of consumer understanding previously identified

Previous studies have shown that consumers find it difficult to understand medical terms.<sup>1-4</sup> A United States (US) researcher asked 145 people waiting in pharmacies to define a list of medical terms and found that overall only 53% of responses were correct.<sup>5</sup> A subset of these terms was chosen to look at the level of understanding amongst New Zealand consumers, and whether this varied between different ethnic groups.

### Pharmacy customers from three ethnic groups surveyed

Three summer students (Maori, Pakeha and Tokelauan) each interviewed approximately 40 males and 40 females from each of these three ethnic groups. There were 244 participants in total, selected from the greater Wellington area including central city and suburbs. The study was conducted between December 2000 and January 2001. It was funded by the Health Research Council and the Health Services Research Centre.

Most participants were recruited off the street. They were all over 15 years of age and had collected a prescription medicine from a pharmacy (for themselves or someone else) in the last 12 months. Participants were asked to define nine terms (see Table 1). The words were placed in simple, non-leading verbal sentences like "This medicine is an antibiotic". Answers were compared with correct definitions used by the US study, and checked by New Zealand pharmacists. There was a range of acceptable answers, e.g. antibiotic could be correctly defined as an agent that fights, kills or treats infections, bacteria, germs or bugs. All answers were coded as either 'correct', 'vague', 'incorrect', or 'no definition' by all four

members of the research team working together.

### Comprehension varies with ethnicity, education and gender

37% of all responses given were correct. Only three words (i.e. orally, allergic, and inflammation) were defined correctly by over half the respondents. Decongestant was the least understood word (5.3% of respondents defined it correctly).

The level of understanding was found to be related to ethnicity. Pakeha respondents gave on average 5.3 correct responses, Maori 3.1 and Tokelauans 1.7. For Tokelauans born in the Tokelau Islands, the figure was particularly low (1.2 correct answers on average). This could be due to English being a second language for most of the older Tokelauans interviewed.

Education also affected the number of correct responses. Participants who had attended a tertiary institution correctly defined an average of 4.2 words; those who had finished their education at secondary school scored 2.6; and those who had only been to primary school could correctly define 1.1 words.

Women could correctly define more of the words than men. On average, female respondents defined 3.8 words correctly, while males defined 2.8.

### Perceived meaning often vastly different from correct definition

Overall, almost a quarter of responses (23.2%) were incorrect. In some of these, participants thought they understood the term but were unable to provide a correct definition. Others attempted to guess the meaning, often choosing words that sounded similar, e.g. diet or diabetes to define diuretic.

**Table 1: Respondents understanding of medical terms (n=244)**

Term	Correct <sup>1</sup> definition (%)	Vague <sup>2</sup> definition (%)	Incorrect <sup>3</sup> definition (%)	No <sup>4</sup> definition (%)
Allergic	59	17	13	11
Orally	67	1	16	16
Cough suppressant	49	20	12	19
Antibiotic	36	13	36	15
Hypertension	22	2	36	40
Antihistamine	29	4	13	55
Diuretic	16	3	21	60
Inflammation	52	5	21	22
Decongestant	5	5	39	50
<b>Total (%)</b>	<b>37</b>	<b>8</b>	<b>23</b>	<b>32</b>

1 = a clear definition given; 2 = explanation incomplete or ambiguous; 3 = erroneous understanding; 4 = no attempt or word not recognised; Note: percentages have been rounded to whole numbers so rows may not total 100.

Common misunderstandings included that to take a medicine orally meant to take it regularly or at a certain time; that antibiotics were painkillers or were used to treat viruses or ‘flu; that having hypertension meant being stressed, tense or hyperactive; that inflammation was the same as infection; and that decongestants cleared the lungs or were for the digestive system.

### Findings show minimal knowledge of common words

The overall level of understanding of these common medical terms was very low, and there were significant differences by ethnicity, education and gender. This could reflect a poor understanding of the English language in general, however some tertiary educated pakeha respondents were unable to correctly define all the terms. This suggests that health professionals need to take care to use everyday language when communicating to consumers, particularly to those for whom English is a second language.

The high level of incorrect answers is particularly worrying. Some consumers believed they understood the words but did not. Other incorrect answers were given by people guessing what a word meant. Possible consequences are that people may adopt this ‘guessing’ strategy in a situation where a health professional uses a word they do not understand. Also, consumers may use these medical words when talking to their doctor, but have a completely different understanding of the words. Both scenarios could lead to potentially harmful misinterpretations.

### Health professionals can minimise misunderstandings by using consumer-friendly language

Even though the sample size was not large, the findings of this study do highlight the importance of using simple, clear language when communicating to consumers. Many of these medicine-related terms are frequently used on the presumption that all consumers comprehend their true meaning. Health professionals have a responsibility to ensure that consumers understand the information given to them. Use language that your patients will comprehend and check that the health information provided has been understood. This will assist patients to understand the treatment regimen that is being recommended, and to be active participants in shared decision-making about their health care.

Further details about this study are available in *New Zealand Pharmacy* 2001;22(4):13-16 and in the *International Journal of Pharmacy Practice* 2001;9:269-274.

Competing interests (authors): none declared.

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## ADVERSE REACTIONS OF CURRENT CONCERN



The Medicines Adverse Reactions Committee (MARC) first initiated the list of *adverse reactions of current concern* in 1994, as a means of bringing particular medicine adverse reactions to the attention of prescribers. The purpose of the list is also to encourage prescribers to report the reactions to the Centre for Adverse Reactions Monitoring (CARM) so that more information can be gathered, and further action taken if necessary. The reports provide a New Zealand perspective on emerging medicine safety issues.

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

Since initiation, the number of reactions listed has grown, and is revised from time to time. Amendments are made either in response to reactions reported in New Zealand or international pharmacovigilance issues. Regular readers will observe that the list of *adverse reactions of current concern* (see page 13) no longer includes cardiac arrhythmia with cisapride, and neutropenia/thrombocytopenia with ticlopidine. The MARC has now added hyperglycaemia with all atypical antipsychotics, and cardiovascular events with COX-2 inhibitors.

### Update

#### **Venous thromboembolism with oral contraceptives**

Oral contraceptives were added to the list of *adverse reactions of current concern* in February 1996<sup>1</sup> after international studies<sup>2-5</sup> found that third generation oral contraceptives (OCs) were associated with a higher risk of venous thromboembolism (VTE), compared to second generation OCs. Since listing, CARM has received 32 reports of pulmonary embolism (nine fatal) and 48 reports of other venous thrombotic events with combined OCs. No fatal cases have been reported since 1999, possibly reflecting reduced prescribing of the third generation OCs, greater attention to risk factors, and higher index of suspicion for early diagnosis and treatment of VTE.

Diane 35/35ED™ (cyproterone acetate and ethinyloestradiol), for use in women with androgenic disorders who require contraception, were added to the list in February 2001 following reports of VTE in women taking Diane-35, in New Zealand (see article on page 2). Estelle 35/35ED™ (a generic brand) were also added to the list of *adverse reactions of current concern* in October 2001.

Prescribers are encouraged to keep reporting VTE with all OCs to CARM as the reactions remain under active surveillance by the MARC.

### Recent deletions

#### **Cardiac arrhythmia with cisapride**

Cisapride was listed in May 1999 following overseas reports of deaths from QT-prolongation, which prompted several countries to withdraw cisapride from the market or restrict its use. Since being listed, there have been no specific local reports of arrhythmia, but one report each of supraventricular tachycardia (SVT) and tachycardia. Prescribing restrictions placed on the use of cisapride during 2000<sup>6</sup> may have contributed to the lack of reactions reported. Cisapride and cardiac arrhythmia is no longer an *adverse reaction of current concern*.

#### **Neutropenia/thrombocytopenia with ticlopidine**

This was added to the list in December 1998, following a case reported to CARM of rapid onset neutropenia caused by ticlopidine. The MARC had also reviewed a study describing 60 cases of thrombotic thrombocytopenic purpura with ticlopidine.<sup>7</sup> Since the listing, there has been only one report of granulocytopenia. No reports of neutropenia have ever been received in New Zealand. Neutropenia/thrombocytopenia with ticlopidine has now been delisted. The low number of reports could be explained by the increasing preferential use of clopidogrel, which has a lower incidence of blood dyscrasias.<sup>8</sup> The CARM database holds three reports for clopidogrel, none of which involve the haematological system.

## Recent additions

### Hyperglycaemia with all atypical antipsychotics

Local and international adverse reaction reports suggest that all atypical antipsychotics (clozapine, olanzapine, quetiapine and risperidone) may be associated with impaired glucose metabolism, causing hyperglycaemia or new onset diabetes mellitus.<sup>9,10</sup> Hence, the MARC has decided to extend the *adverse reaction of current concern* of hyperglycaemia with clozapine to include all of the atypical antipsychotics.

In February 2002, the CARM/IMMP database held four reports of diabetes mellitus or hyperglycaemia with clozapine, two reports of diabetes mellitus with olanzapine and one of hyperglycaemia with risperidone. Up to the same date the numbers of reports of these events, plus aggravated or reactivated diabetes mellitus, in the WHO database were 616 for clozapine, 391 for olanzapine, 18 for quetiapine and 141 for risperidone.

### Cardiovascular events with COX-2 inhibitors

There is some preliminary evidence, needing confirmation, that the COX-2 inhibitors (celecoxib and rofecoxib) may be associated with cardiovascular events. The first indication of this association came from a surprise result of the

VIGOR study<sup>11</sup> in which 0.4% of the rofecoxib group and 0.1% of the naproxen group developed myocardial infarction. This result was extended by a between-study comparison conducted by Mukherjee et al.<sup>12</sup> The comparison, which included celecoxib and rofecoxib, implicated both medicines as being associated with a significantly higher rate of myocardial infarction than placebo. These authors postulated that COX-2 inhibitors may have a prothrombotic effect through inhibition of prostacyclin.<sup>12</sup>

As at January 2002, 8% of the celecoxib reactions reported to CARM and 15% of those for rofecoxib were of cardiovascular events. Although rofecoxib and celecoxib are being monitored in the IMMP, the interest in the cardiovascular effects of these medicines is such that the MARC decided to include them in the list of *adverse reactions of current concern*.

Please report **all cases** of adverse reactions in the table below, to the Centre for Adverse Reactions Monitoring (CARM), PO Box 913, Dunedin. The reporting form inside the back cover of *Prescriber Update* can be used, or the form downloaded from either the CARM or Medsafe web sites: [www.otago.ac.nz/carm](http://www.otago.ac.nz/carm) or [www.medsafe.govt.nz/Profes/adverse.htm](http://www.medsafe.govt.nz/Profes/adverse.htm)

Medicine/s	Adverse reactions of current concern	Prescriber Update reference
<b>Celecoxib</b>	<b>cardiovascular events</b>	<b>This issue (see above)</b>
Celecoxib-warfarin interaction	increase in INR / haemorrhage	No.22, Oct 2001
<b>Clozapine and all other atypical antipsychotics</b>	<b>hyperglycaemia</b>	<b>This issue (see above) &amp; No.18, Jun 1999</b>
Diane-35™ and 35 ED™	venous thromboembolism	No.20, Feb 2001
Estelle-35™ and 35 ED™	venous thromboembolism	No.22, Oct 2001
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
<b>Rofecoxib</b>	<b>cardiovascular events</b>	<b>This issue (see above)</b>
Rofecoxib-warfarin interaction	increase in INR / haemorrhage	No.22, Oct 2001

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## 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.

### 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 the Centre for Adverse Reactions Monitoring (CARM), PO Box 913, Dunedin. The reporting form inside the back cover of *Prescriber Update* can be used, or the form downloaded from either the CARM or Medsafe web sites: [www.otago.ac.nz/carm](http://www.otago.ac.nz/carm) or [www.medsafe.govt.nz/Profs/adverse.htm](http://www.medsafe.govt.nz/Profs/adverse.htm)

The medicines currently being monitored are (no changes since the October 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
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 / 5HT <sub>2</sub> blocker
Olanzapine	Zyprexa	atypical antipsychotic
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

**Follow-up only:**

New patients are no longer being added to the cohorts for copper IUCD (Multiload Cu 375™), eformoterol (Foradil™, Oxis™) and salmeterol (Serevent™). However, follow-up of existing patients is continuing.

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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**<sup>1</sup>

Report all adverse reactions to **new medicines** and **all** events to **IMMP medicines**.<sup>2</sup>

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 form overleaf or the card supplied with *New Ethicals Catalogue*.

**Or:** The form can be downloaded from [www.otago.ac.nz/carm](http://www.otago.ac.nz/carm) or  
[www.medsafe.govt.nz/profs/adverse.htm](http://www.medsafe.govt.nz/profs/adverse.htm)

**Mail the form to:** Freepost 112002  
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**Or fax it to:** (03) 479 7150

**Phone:** (03) 479 7247

**Email:** [carmnz@stonebow.otago.ac.nz](mailto:carmnz@stonebow.otago.ac.nz)

**Web site:** [www.otago.ac.nz/carm](http://www.otago.ac.nz/carm)

1. The list of adverse reactions of current concern is on page 13.
2. The list of medicines in the Intensive Medicines Monitoring Programme (IMMP) is on page 15.