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FROM THE EDITOR

Prescribers – don't miss out!

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

Medicine quality problems – please alert Medsafe

Prescribers and pharmacists are asked to inform Medsafe directly of problems with the quality or safety of medicines and medical devices as soon as they become apparent, so that remedial action can be taken. Medsafe has the authority to request that pharmaceutical sponsors address problems such as therapeutic failure and physical defects (e.g. increased friability). This may result in a product recall, issue of warnings to health professionals and consumers, reformulation or redesign of the product, or alternative suppliers being sought.

If you are aware of any problem (however minor or infrequent) regarding the quality of a medicine or medical device, please report this in the first instance to the Compliance Team at Medsafe (phone 04 496 2573), who will investigate the matter. Adverse events arising from brand switching, including lack of efficacy, should be reported to CARM in Dunedin (phone 03 479 7247).

Key to Prescriber Update articles

To assist readers in knowing the origin of articles published by Medsafe, the symbols below will appear next to the article title, where applicable. It is our editorial policy to ensure that articles displaying either of these symbols have undergone independent peer review. During the development of an article, the pharmaceutical company supplying the medicine referred to in the article may be given the opportunity to comment on the draft.

ADR UPDATE

Adverse Drug Reaction Update articles are written in response to adverse reaction reports lodged with the Centre for Adverse Reactions Monitoring (CARM) and material in the international literature. These articles may also be written to alert prescribers and pharmacists to potential problems with medicines.

MARC Rx ADVICE

MARC Prescribing Advice articles are recommendations from the Medicines Adverse Reactions Committee (MARC) in response to medicine safety issues and overseas experiences.

Free resources for health professionals

In June 2001, Medsafe distributed **Consumer Medicine Information (CMI) posters** to all pharmacies and prescribers. CMI is written information for consumers. Some consumers have commented to Medsafe that the CMI poster is not displayed in pharmacies or surgery waiting rooms. If you would like to obtain another copy of this poster, contact Wickliffe (details below).

Please inform your patients about the CMI available (at no charge) on the Medsafe web site. You can either direct patients to www.medsafe.govt.nz or access the CMIs yourself at this web address.

The *Code of Health and Disability Services Consumers' Rights* (a regulation under the Health and Disability Commissioner Act 1994) confers a number of rights on all consumers of health and disability services in New Zealand, and places corresponding **obligations on** providers of those services, i.e. all registered **health professionals** such as yourself. Providing medicines information to your patients and informing them about the availability of CMI helps you meet your obligations under this Code.

Along with the CMI poster, Medsafe supplied a complimentary copy of the **Prescribing Medicines in Pregnancy booklet** (4th edition). Additional copies may be obtained from Wickliffe.

In March this year, Medsafe updated and distributed the **patient information leaflet on oral contraceptives** and blood clots. Bulk copies are still available, at no charge, from Wickliffe.

To order copies of these resources, contact Wickliffe: phone 04 496 2277, fax 03 479 0979 or email pubs@moh.govt.nz

HORMONE REPLACEMENT THERAPY – RAPID REVIEW

MARC Rx ADVICE

In September 2002, Medsafe sent a letter about the safety of HRT to all doctors and pharmacies. It was accompanied by updated key messages on HRT prescribing from the New Zealand Guidelines Group (copies of both documents are available on the Medsafe web site at www.medsafe.govt.nz/hot/contraceptives.htm). The article below provides background information about the advice given in the Medsafe letter.

At its meeting of 11 September 2002, the Medicines Adverse Reactions Committee (MARC) reviewed studies examining the safety of hormone replacement therapy (HRT). On completion of its review, the MARC concluded that HRT provides a number of benefits with respect to control of symptoms associated with oestrogen deficiency, such as flushing and night sweats, and in preventing loss of bone density. However, for most women the risks associated with long-term use of HRT outweigh the benefits.

These risks include:

- An immediate increase in the risk of venous thromboembolism (VTE) for all HRT products containing oestrogen. The increase in relative risk seen for all forms of HRT is of a similar size to that seen for oral contraceptive pills. Given that the baseline risk of VTE increases with age, the absolute risk is larger than for oral contraceptives.
- An increase in the risk of stroke that becomes statistically significant beyond 2-3 years use of combined HRT.
- An increase in the risk of developing breast cancer that becomes evident following prolonged use (more than 4-5 years). While the increase in risk is small, it has been confirmed by several studies and applies to all forms of HRT. There is insufficient information available to determine how long the increased risk of breast cancer persists after cessation of HRT.
- A possible increase in the risk of coronary heart disease. The data clearly indicated that despite evidence of HRT lowering cholesterol levels in treated patients, use of combined HRT neither prevents nor inhibits the further progression of coronary heart disease. The MARC considered that the totality of research indicates that combined HRT may possibly increase the risk of developing coronary heart disease.

In the opinion of the MARC, the increased risk of breast cancer and stroke means that the benefit:risk ratio for combined HRT products becomes unacceptable for most women after about 3 to 4 years duration of use.

To improve the safe use of HRT, the MARC recommends that:

- HRT should normally be used only where menopausal symptoms are disruptive to the quality of life of the woman;
- HRT should not be used for the primary or secondary prevention of coronary heart disease or stroke;
- In most circumstances, the risks of long term treatment outweigh the benefits; and combined HRT generally should not be used for longer than 3-4 years;
- Oestrogen-only HRT increases the risk of breast cancer and venous thromboembolism to a similar extent as combined HRT;
- All prospective and current users of HRT should be advised of the risks and benefits of oestrogen and progestogens;
- The need for continued treatment with HRT should be reviewed at the woman's next visit to her General Practitioner and thereafter on a yearly basis.

Further information on the risks and benefits of HRT is described in the following article recently published in *The Lancet*, reprinted below with permission from Elsevier Science (*The Lancet* 2002;360:942-944). The MARC reviewed an advance copy of this paper and concluded that it provides a balanced and reliable overview of the available data on the risks and benefits of HRT.

Evidence from randomised trials on the long-term effects of hormone replacement therapy

Valerie Beral, Emily Banks, Gillian Reeves; Cancer Research UK Epidemiology Unit, Oxford, United Kingdom

Reprinted from *The Lancet* 2002:360:942-944 with permission from Elsevier Science.

Context Over the past few decades hormone replacement therapy (HRT) has been used increasingly by postmenopausal women in western countries. The need for objective data on long-term effects prompted the setting up of randomised trials to compare cancer and cardiovascular disease endpoints in HRT users and non-users. With the early termination of part of the Women's Health Initiative trial (*JAMA* 2002; 288: 321-33), it is timely to review the evidence from such studies.

Starting point Four randomised trials including over 20 000 women followed up for 4·9 years, on average, have now reported on the effect of HRT for major, potentially fatal, conditions. Overall, HRT users had a significantly increased incidence of breast cancer, stroke, and pulmonary embolism; a significantly reduced incidence of colorectal cancer and fractured neck of femur; but no significant change in endometrial cancer or coronary heart disease. There was no significant variation across the trials in the results for any condition. Three trials had recruited women with previous cardiovascular disease and the fourth, the Women's Health Initiative, had recruited healthy women. Combined oestrogen/progestagen HRT was used in three trials and oestrogen alone in one. Use of HRT over a 5-year period by healthy postmenopausal women in western countries is estimated to cause an extra breast cancer, stroke, or pulmonary embolus in about 6 per 1000 users aged 50-59 and 12 per 1000 aged 60-69. Over the same period, the estimated reduction in incidence of colorectal cancer or fractured neck of femur is 1·7 per 1000 users aged 50-59 and 5·5 per 1000 aged 60-69. The increased incidence of any one of these conditions is greater than any reduction, the estimated net excess over 5 years being 1 per 230 users aged 50-59, and 1 per 150 aged 60-69.

Where next Substantial new data should soon be available from randomised trials of oestrogen-alone HRT versus placebo, whereas few additional trial data on combined HRT are expected for about a decade. Existing randomised trials are too small to describe reliably the effect of HRT on important but rarer conditions, such as ovarian cancer, or on cause-specific mortality. Nor will they provide information about other types of oestrogen or progestagen. Answers to such questions will require judicious analysis and interpretation of data from observational studies.

Use of hormone replacement therapy (HRT) has increased among postmenopausal women in western countries: an estimated 20 million women worldwide were using HRT in the late 1990s.[1] The long-term effects of HRT on cancer and cardiovascular disease have been debated since HRT was first prescribed, and various randomised trials were designed to provide reliable unbiased information on the incidence of these outcomes (panel 1).[2-11] Four of these trials,[2,3,7,8] two of which ended prematurely,[2,7] have published their main results (the Women's Health Initiative [WHI][2-11] published results for part of the trial only). We review findings for seven major, potentially fatal, conditions that were primary or secondary outcomes: cancer of the breast, endometrium, and colorectum; coronary heart disease; stroke; pulmonary embolism; and fractured neck of femur (see methods in appendix at http://image.thelancet.com/extras/02art8214webappendix.pdf).

The four trials with published results included over 20 000 postmenopausal women, followed for 4·9 years, on average (panel 1). The active treatment was combined oestrogen/progestagen in three trials[2,3,7] and oestrogen-alone in one (WEST).[8] Three trials recruited women with previous cardiovascular disease and WHI recruited healthy women. Overall, for women randomised to HRT compared with placebo, there was: a significant excess of breast cancer (relative risk 1·27, 95% CI 1·03-1·56), stroke (1·27, 1·06-1·51), and pulmonary embolism (2·16, 1·47-3·18); a significant

deficit of colorectal cancer (0·64, 0·45-0·92) and fractured neck of femur (0·72, 0·52-0·98); but no overall significant excess or deficit for endometrial cancer (0·76, 0·45-1·31) or coronary heart disease (1·11, 0·96-1·30) (figure).

There was no significant heterogeneity in any of these results across the trials, suggesting that the relative risks associated with the use of HRT do not vary substantially across women with different underlying risks of cardiovascular disease or using different hormonal preparations.

What has been learnt from the trials?

Results from randomised trials broadly agree with findings from observational studies for cancer of the breast and colorectum,[1,12] and also for pulmonary embolism[13] and fractured neck of femur.[14] Moreover, the WHI reported an increasing risk of breast cancer over time,[2] corresponding to the increasing risk of breast cancer with duration of use of HRT found in observational studies.[12] Both trial and observational data showed that the risk of venous thromboembolism was greater soon after starting HRT than in later years.[2,3,13] Since objective trial data have confirmed previous observations for these conditions, we can conclude that the findings are true effects of HRT, and not due to bias or confounding.

By contrast, the results from many observational studies, suggesting that both combined oestrogen/progestagen and oestrogen-alone HRT substantially reduce the risk of coronary heart disease, must now be regarded as severely biased. Many commentators had argued that the lower rates of coronary heart disease among HRT users compared with non-users found in observational studies did not necessarily mean that HRT protected against the disease (appendix).[1,11,13] It was the need for unbiased data on the incidence of coronary heart disease that prompted the setting up of most of the randomised trials. Unexpectedly, results from HERS suggested an adverse effect of HRT on coronary disease in the first year after randomisation[3,4] and findings from WHI were in a similar direction, but not significant.[2] Nevertheless, neither trial has shown long-term benefit for coronary disease.[2,3,4] Given the consistent evidence from all trials of little or no benefit, previous claims that HRT substantially protects against coronary heart disease should now be discounted. The increased incidence of

Panel 1: **Randomised trials of HRT versus placebo (n≥100) set up to study cancer and cardiovascular disease as endpoints**

Study	Women recruited	Number*/ follow-up (yrs)	Active treatment (orally per day)	Comments
Heart and Estrogen/progestagen Replacement Study (HERS)[3-6]	With previous heart disease	2763 / 4·1	0·625 mg equine oestrogen and 2·5 mg MPA	Multicentre USA; main results published.[3-6,19]
Estrogen in Venous Thromboembolism Trial (EVTET)[7]	With previous VTE	140 / 1·3	2 mg estradiol and 1 mg norethisterone acetate	Norway; terminated early, after reports that HRT increased VTE risk; VTE results published.[7]
Women's Estrogen for Stroke Trial (WEST)[8]	With previous stroke	664 / 2·8	1 mg 17ß-oestradiol	Multicentre USA; main results published.[8]
Women's Health Initiative (WHI)[1,11]	(a) Healthy women with intact uterus	16 608 / 5·2	0·625 mg equine oestrogen and 2·5 mg MPA	Multicentre USA; terminated early; main results published.[1]
	(b) Healthy women without uterus	10 739 / 8 (planned)	0·625 mg equine oestrogen	Multicentre USA; due to end 2005; no results yet.
Oestrogen in the Prevention of Re-Infarction Trial (ESPRIT-UK)[9]	With first myocardial infarction	1017 / 2 (planned)	2 mg oestradiol valerate	UK; due to end in 2002; no results yet.
Women's International Study of Long Duration Oestrogen after the Menopause (WISDOM)[10]	Healthy women	~22 000 / 10 (planned)	As for WHI, except 0·625 mg equine oestrogen and 2·5 mg MPA also used in hysterectomised women	UK, Australia, New Zealand; due to end 2012; no results yet.

*Approximately equal numbers randomised to placebo and active treatment in each trial. MPA=medroxyprogesterone acetate, VTE=venous thromboembolism.

stroke among HRT users in the randomised trials is a new finding. Results from observational studies were mixed[13] but now that there is consistent trial evidence of an increase for all strokes combined, the effect of HRT on subtypes of stroke warrants further investigation.

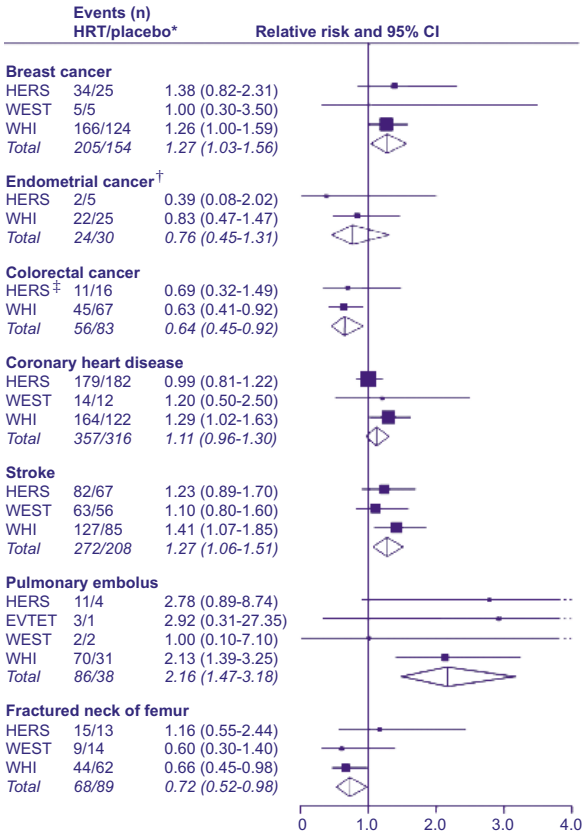
No trial was designed with all-cause mortality as an endpoint, as it is an insensitive marker of any specific effect of HRT. The fact that the trials found no change in all-cause mortality (relative risk 1·03, 95% CI 0·90-1·18, for all trials combined) merely means that HRT does not have an immediate, substantial, and non-specific effect on mortality. Unfortunately, the trials are too small to provide much-needed reliable evidence about the effects of long-term HRT on cause-specific mortality (see appendix).

Implications of the trials for HRT users

Combined HRT, containing conjugated equine oestrogen and medroxyprogesterone acetate, was selected for study in the largest trials[2,3,10] because these were the most commonly used constituents of HRT in the USA when the trials were set up. At that time, the available evidence suggested that the effects of particular types or combinations of oestrogen or progestagen did not differ materially, with the exception of the greater risk of endometrial cancer with oestrogen-alone than oestrogen/progestagen combinations.[11] There is no trial evidence to contradict this view, although the power to detect such differences is limited.

The cause-specific relative risks in the trials did not differ significantly for women with varying background risks of disease or personal characteristics, including different ages, ethnic groups, smoking patterns, and previous illnesses and users of various medications.[2-6] Thus the results are generally applicable to postmenopausal women.[2] We have, therefore, estimated the change in age-specific incidence of conditions significantly associated with HRT, for healthy postmenopausal women in western countries who use HRT for 5 years (panel 2 and appendix). The estimated excess incidence of breast cancer, stroke, and pulmonary embolism is greater than the estimated deficit of colorectal cancer and hip fracture, and the net excess is greater at age 60-69 (1 extra event per 150 HRT users) than 50-59 (1 per 230). At age 50-59, when use of HRT is most prevalent,[1] breast cancer makes the greatest contribution to the excess, whereas cardiovascular disease becomes increasingly important at older ages.

The estimates of excess risk provide, at best, a rough guide to the likely change in incidence for these conditions over a 5-year period for typical HRT users in western countries. Equal weight was given to each condition, whereas individuals have varying background risks for each disease, and may well assign different weights to their importance, as well as to the relief of menopausal symptoms. No attempt was made to estimate mortality or lifetime risk, since little is known about case-fatality or the persistence of the effects of HRT. Yet such information is vital, because for example, the incidence of certain conditions, such as vertebral fracture and other severe complications of osteoporosis, increases sharply with age. As for some other outcomes, the largest double-blind randomised trials to date suggest that



Summary of results for seven major conditions in trials of HRT
Tests for heterogeneity: breast cancer (χ^2_2=0·24, p=0·9), endometrial cancer (χ^2_1=0·75, p=0·4), colorectal cancer (χ^2_1=0·04, p=0·8) coronary heart disease (χ^2_2=2·81, p=0·2), stroke (χ^2_2=1·26, p=0·5), pulmonary embolus (χ^2_3=0·74, p=0·8), fractured neck of femur (χ^2_2=1·98, p=0·4). *Equal numbers randomised to HRT and placebo in each trial; †results for WEST (2/0) not included, as oestrogen alone has different effect from oestrogen/progestagen on endometrial cancer; ‡colon cancer only.

Panel 2: **Estimated change in incidence of major, potentially fatal, conditions in 1000 healthy postmenopausal women from western countries using HRT over 5-year period, based on results from randomised trials (see appendix for methods)**

	Women aged ~50-59 years	Women aged ~60-69 years
Excess incidence per 1000 HRT users, over 5-year period, for:		
Breast cancer	3·2	4·0
Stroke	1·2	4·0
Pulmonary embolism	1·6	4·0
*Total excess**	*~6 per 1000, ~1 in 170 users*	*~12 per 1000, ~1 in 80 users*
Reduction in incidence per 1000 HRT users, over 5-year period, for:		
Colorectal cancer	1·2	3·0
Fracture of neck of femur	0·5	2·5
*Total deficit**	*~1·7 per 1000, ~1 in 600 users*	*~5·5 per 1000, ~1 in 180 users*
Overall balance*	**Net excess:** *~4·3 per 1000, ~1 in 230 users*	**Net excess:** *~6·5 per 1000, ~1 in 150 users*

*Giving equal weight to each type of event.

HRT does not slow the progress of Alzheimer's disease or improve cognitive function,[15] and that it has little effect, if any, on quality-of-life other than reducing menopausal symptoms.[16]

The future

New results on about 12 000 women randomised to oestrogen-alone versus placebo are expected soon, from ESPRIT-UK[9] and part of WHI[2] (panel 1). The data for combined HRT reviewed here are, however, unlikely to be superceded in the immediate future. Results from WISDOM,[10] which is randomising about 22 000 healthy women to similar oestrogen/progestagen combinations as WHI, are not expected for a decade. These trials are also studying the effect of HRT on quality-of-life and cognitive function.

Existing trials are too small to provide reliable information on other important, but rarer conditions, such as ovarian cancer,[17] or on cause-specific mortality. Nor are they examining the effects of other specific types of oestrogen and progestagen used in HRT formulations. Observational studies will thus be needed to answer many outstanding questions about the effects of HRT. Judicious data analysis and interpretation of results will be essential.

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AVOIDING TERATOGENICITY WITH ISOTRETINOIN

ADR UPDATE

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

The teratogenicity of isotretinoin is well documented. The first New Zealand case of embryopathy was recently reported to CARM. This is a timely reminder that effective contraception is recommended for all women of childbearing age for whom isotretinoin is a treatment option. It is also important to exclude pregnancy prior to starting isotretinoin, and for women to continue contraception for one month after stopping isotretinoin.

Isotretinoin known to cause severe foetal malformations

Isotretinoin (Oratane™, Roaccutane™) is classified as Category X under the Australian categorisation of risk of medicine use in pregnancy, meaning the medicine has such a high risk of causing permanent damage to the foetus that it should not be used in pregnancy or where there is a possibility of pregnancy.[1] In humans, isotretinoin can cause central nervous system malformations, absence or deformity of ears, cleft palate, cardiac and great vessel defects, and eye abnormalities.[2,3] These abnormalities occur at various dosages within the usual therapeutic range and have occurred in women who were treated for less than one week in the first trimester of pregnancy. This suggests that a single dose of isotretinoin may be teratogenic.[4]

First NZ report of isotretinoin associated embryopathy

The Centre for Adverse Reactions Monitoring (CARM) has recently received its first report of embryopathy in association with a patient taking isotretinoin in New Zealand. The woman had been taking isotretinoin 40 mg/day for three months when she became pregnant. It is unknown whether she was using contraception. When the woman stopped isotretinoin, she was six weeks pregnant. Antenatal ultrasound showed no abnormalities but the child was born with typical retinoid embyropathy including heart, ear and oesophageal malformations. The World Health Organisation database has 691 reports of foetal disorders associated with isotretinoin, including 35 of multiple malformations.

High incidence of severe malformations seen in US study

In a large study[4] of 433 spontaneous reports of women exposed to isotretinoin during pregnancy in the United States, 130 patients (or a third of 396 reports in whom timing of conception was known) were already pregnant when they started isotretinoin. An additional 65 patients became pregnant in the first three weeks of isotretinoin use. Pregnancy outcomes were known in 409 pregnancies. Among these, 54% ended in elective abortion and 7% in spontaneous or missed abortion. Of 151 births, 48% were normal, 47% had congenital malformations, and 5% had abnormalities other than malformations.

Implement precautions to avoid pregnancy in women using isotretinoin

Isotretinoin is known to be highly teratogenic, therefore it is important to prevent pregnancy occurring during (and immediately after) isotretinoin use. It is essential that all female patients be counselled about the very significant risk of teratogenicity. The following approach is recommended when prescribing isotretinoin to **all** women of childbearing potential.[5] These precautions are also advised for women who do not usually use contraception because of a history of infertility.[2,3]

1) Take a current sexual history. No assumptions should be made on the basis of age, race or religious beliefs, although clinicians should be sensitive to such issues. It may be necessary to conduct some of this enquiry with the patient alone, in the absence of parents and partners.

2) A menstrual history should be taken: patients with irregular menses present a difficult management problem.

3) Before starting isotretinoin treatment, all female patients of childbearing potential should have a pregnancy test, preferably but not essentially performed on blood since it is more accurate at an earlier stage of pregnancy.

4) An appropriately trained clinician (not necessarily the dermatologist) should advise the woman about effective contraception. The physician prescribing the isotretinoin needs to ensure that the woman understands the importance of using contraception during treatment and is agreeable to doing so. Emergency contraception is an option, should it be required, but this must not be the regular method of contraception.

5) One month before starting isotretinoin commence the woman on contraception, ideally hormonal such as either a combined oral contraceptive pill, or an injectable or implantable hormonal contraceptive. Intra-uterine devices are also an option. The progesterone-only pill may be less reliable in women taking isotretinoin.

6) Dermatologists should ensure that all female patients who are *at risk of pregnancy* fully understand the risks of pregnancy, are not currently pregnant and have been using appropriate contraception for one month before starting treatment, and that the responsibilities of the patient and physician have been discussed. This includes advising the patient that they are responsible for consulting their GP, Family Planning clinic or dermatologist, if they have knowingly had unprotected intercourse (or when contraceptive failure is suspected) so that the possibility of using emergency contraception can be considered.

7) Isotretinoin treatment should ideally begin with the patient's next menstrual cycle.

8) Regular pregnancy tests should be undertaken during treatment with isotretinoin.

9) Contraception should be continued for one month after stopping isotretinoin.

Competing interests (author): none declared.

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AGITATION, RESTLESSNESS AND SUICIDAL BEHAVIOUR WITH FLUOXETINE, PAROXETINE AND SERTRALINE

ADR UPDATE

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

There have been rare reports of fluoxetine and, more recently, paroxetine and sertraline being associated with aggressive or suicidal thoughts and behaviour. Due to similar pharmacological profiles, the same reactions may occur with other selective serotonin re-uptake inhibitors (SSRIs). It is possible that these adverse events can be attributed to akathisia (involuntary severe motor restlessness). However, the most common reason for self-harm behaviour during treatment with any antidepressant is worsening depression. The development of severe agitation or self-harm behaviour is an indication that the patient and their antidepressant therapy require prompt review. Patients should be advised to seek medical attention as soon as possible if they develop agitation or restlessness, or if their depression worsens.

Reports of aggressive and suicidal behaviour with SSRIs investigated

Soon after the introduction of fluoxetine internationally, it was claimed to cause suicidal thinking and behaviour.[1] This allegation was investigated by a number of regulatory agencies, including the Food and Drug Administration in the United States in 1991, and was not substantiated. More recently, there have been several further case reports, some given media prominence, and some leading to legal proceedings, not only in relation to fluoxetine[2,3] but also to paroxetine and sertraline.[4-6] Systematic reviews continue to support the view that selective serotonin re-uptake inhibitors (SSRIs) are effective and are not associated with increased suicidality or increased violence.[7] However, these reports[1-6] raise questions about whether the small group of patients experiencing the rare side effect of akathisia are at increased risk of suicide.

Behaviour change may be due to SSRI-induced akathisia

Detailed case reports[1,4] describe the emergence of marked restlessness and agitation, followed by suicidal thinking or behaviour, in patients soon after commencing fluoxetine or other serotonergic agents. This restlessness and agitation may reflect akathisia (involuntary severe motor restlessness). Although more commonly associated with antipsychotics, reflecting dopamine receptor blockade, interactions between the serotonergic and dopaminergic systems may account for akathisia also occurring with SSRIs.[8-10] A putative link between akathisia and suicidal behaviour is less clear, and not all of the more recent case reports describe preceding restlessness.[1,4] Older groups of antidepressants have also been associated with increased suicidal thinking and behaviour, although not related to increased restlessness.[11]

Agitation or harmful behaviour signals need to review both patient and treatment immediately

The key issues in treating depression are the selection of an appropriate treatment in conjunction with the depressed person, and the use of an adequate dose for an adequate length of time, along with attention to current stressors. The most common reason for suicidal ideation or behaviour during treatment with any antidepressant remains worsening depression. The development of agitation or self-harm behaviour (from any cause) indicates the need to increase support to ensure the patient's safety, as well as a review of treatment to check that it is optimised for that person.

Informing patients to seek help may help reduce adverse outcomes

As with many medicines, rare serious side effects may emerge during treatment and patients should be aware of these and what action to take. It is recommended that all patients taking SSRIs should be advised that if they become particularly agitated or restless, they should seek medical advice and stop their antidepressant in the interim. In addition, any serious worsening of their symptoms, particularly in relation to suicidal thoughts, should be reported urgently to their treating doctor (or on-call colleague). Severe agitation, severe restlessness/akathisia, and/or increased suicidality with SSRIs have been added as *adverse reactions of current concern* (see page 44).

Competing interests (author): the author is supervising a PhD student whose research has been funded by Eli Lilly. He has accepted invitations from pharmaceutical companies to speak at several meetings relating to prescribing in general, as well as other topics. He has a beneficial interest in shares of certain pharmaceutical companies, including some who manufacture antidepressants, including SSRIs.

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OMEPRAZOLE MAY ELEVATE CLOZAPINE LEVELS

Dr David Coulter, IMMP Director, Centre for Adverse Reactions Monitoring, Dunedin

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The IMMP has received three reports of elevation of clozapine levels occurring when omeprazole was co-prescribed in patients already stabilised on clozapine. In two of the cases seizures occurred. The mechanism of the interaction is unknown, but it would be prudent to monitor clozapine levels if concurrent therapy with omeprazole is necessary.

Three reports have been received in the Intensive Medicines Monitoring Programme (IMMP) of problems associated with the combined use of clozapine (Clopine™, Clozaril™) and omeprazole (Losec™). The dose of omeprazole was unknown in each case. The reports are summarised as follows.

1. A man aged 73 was well stabilised after titration of clozapine to 200mg daily. At 150mg daily, he had a blood level of clozapine of 570 nmol/L. Omeprazole was added to his therapy and about two months later his clozapine blood level was 2700 nmol/L. This rose to 6420 nmol/L after a further six days (usual therapeutic range 1-2000 nmol/L). No adverse effects were reported. The dose of clozapine was reduced and plasma levels fell quite quickly.
2. A man aged 32 had remained well on clozapine 475mg daily, for three years. Some time after commencing omeprazole, he was found unconscious after a probable seizure. A high clozapine plasma level (8216 nmol/L) was noted. Clozapine was withdrawn for four days to reduce plasma levels, and the patient recovered.
3. Another man aged 44 had been well controlled on clozapine 600mg daily for two years, and was then prescribed omeprazole for peptic ulceration and oesophagitis. Two weeks later he suffered a generalised seizure and had a plasma clozapine level of 1790 nmol/L. No previous values were available. The omeprazole was discontinued and the clozapine dose reduced to 300mg daily. There were no further problems.

These reports suggest that the addition of omeprazole to therapy with clozapine may cause elevated clozapine plasma levels and dose-related adverse effects. There is no clearly recognisable mechanism for this interaction. Clozapine and omeprazole have multiple metabolism sites but are both substrates for the CYP 3A4 hepatic enzyme, which may be more important for metabolism in some patients. In these circumstances competitive inhibition may come into play.

Prescribers should be aware of the possibility of this interaction and check clozapine levels if concomitant therapy with omeprazole is required.

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

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PROGESTOGEN-ONLY EMERGENCY CONTRACEPTION AND ECTOPIC PREGNANCY

ADR UPDATE

Dr Mira Harrison-Woolrych, Senior Research Fellow, Centre for Adverse Reactions Monitoring, Dunedin

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

Pregnancies occurring in women using daily progestogen-only oral contraceptive pills are more likely to be ectopic than pregnancies in users of other contraceptive methods. The Centre for Adverse Reactions Monitoring has received three reports of ectopic pregnancy following use of a progestogen-only emergency contraceptive pill. This is a reminder that women who have amenorrhoea (or other symptoms suggestive of pregnancy) following use of progestogen-only emergency contraception should have a pregnancy test. If the result is positive, the possibility of ectopic pregnancy should be considered.

Physiological effects of progestogens may explain higher ectopic pregnancy risk

Low-dose daily progestogen-only oral contraceptive pills are effective at preventing pregnancy but if this method fails, pregnancies are more likely to be ectopic than those occurring among users of other contraceptive methods.[1] A possible explanation is that progesterone modifies tubal function, reduces contractility and thus slows the rate of ovum or blastocyst transport. By the same mechanism, ectopic pregnancies might occur following treatment failure with a progestogen-only emergency contraceptive pill (ECP). The ECP is indicated for the prevention of pregnancy if taken within 72 hours of unprotected intercourse. In New Zealand, there are two brands of progestogen-only ECP available (Levonelle™ and Postinor-2™), both of which contain levonorgestrel.

CARM reports of ectopic pregnancy following progestogen-only ECP use

The Centre for Adverse Reactions Monitoring (CARM) has received three reports of ectopic pregnancy following use of a progestogen-only ECP. In all three cases it appears the post-coital contraception was taken as directed, and in two cases it was reported that treatment was started within 24 hours of unprotected intercourse. In one case, the patient had no other risk factors for ectopic pregnancy and had previously delivered two babies.

ECP more effective when taken sooner

A World Health Organisation (WHO) trial[2] found the progestogen-only ECP method to be more effective and safer than the previous Yuzpe regimen of using combined oral contraceptives for emergency contraception. However, the progestogen-only ECP is not always 100% effective, with efficacy being higher the sooner it is taken after unprotected intercourse (see table below). It is therefore important to encourage women to seek emergency contraception as early as possible, and also to advise them that treatment failure may occur. Women who have amenorrhoea (or other symptoms suggestive of pregnancy) following ECP use should be followed up so that pregnancy can be excluded.

Effect of coitus-to-treatment interval on efficacy of progestogen-only ECP (levonorgestrel 0.75mg)[2]

Time taken after intercourse	Proportion of pregnancies prevented
24 hours or less	95%
25-48 hours	85%
49-72 hours	58%

The possibility of ectopic pregnancy should always be considered

One published review[1] puts the total incidence of ectopic pregnancy in the United States at about 17 per 1000 reported pregnancies. Ectopic pregnancy is a potentially life-threatening condition, which should always be considered in any woman of reproductive age who presents with amenorrhoea (or abnormal vaginal bleeding) and pelvic pain or, more seriously, collapse. Women with these symptoms should have a pregnancy test performed. If this is positive and recent use of the ECP or other progestogen-only oral contraceptives has occurred, the index of suspicion is high for ectopic pregnancy.

Prescribers are also reminded to advise women about the possibility of ectopic pregnancy if contraceptive failure occurs with any oral progestogen-only method, and the importance of promptly seeking medical help if symptoms suggestive of ectopic pregnancy develop.

Competing interests (author): none declared.

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ASTHMA THERAPY AWARENESS STRATEGY

PHARMAC is a stakeholder in a campaign strategy to encourage the use of low dose steroids and the appropriate use of long-acting beta agonists. PHARMAC is aware that there has been a great deal of confusion over which inhaled corticosteroids (ICS) are to be available, and this has been further complicated by recent clinical evidence showing that ICS dosages have been too high both internationally and in New Zealand. For these reasons, from November 2002, PHARMAC is launching a campaign to encourage the appropriate dosage of ICSs. Preparation of this campaign has required input from a number of asthma groups and key experts in the field. It will involve both health professionals and the public.

The key messages are that:

- Fluticasone, beclomethasone and budesonide are all available, although the brand names may have changed. In addition, eformoterol is available with minimal restriction, and salmeterol is available on Special Authority.
- For the vast majority of patients the maximum effective dose of ICS is in the range of 400-800 mcg of beclomethasone or budesonide per day, which is equivalent to 250-500 mcg of fluticasone per day.

ORAL CONTRACEPTIVES, HPV AND RISK OF CERVICAL CANCER

MARC Rx ADVICE

Dr Natasha Rafter, Public Health Registrar, Auckland University

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

An analysis of case-control studies has found that use of oral contraceptives for ≥ 5 years in women with human papillomavirus (HPV) infection is associated with an increased risk of cervical cancer. This confirms existing knowledge and emphasises the need for regular cervical screening of all women aged 20-69 years who have ever been sexually active.

Not all HPV infection is persistent or leads to cancer

The presence of human papillomavirus (HPV) infection is known to play the major causative role in cervical cancer. However, the development of such cancer is multi-factorial and HPV infection alone is not thought to be sufficient.[1,2] More than 30 HPV types infect the genital tract, and these have been classified as either low or high risk types according to the potential of infected cells to progress to carcinoma.[3] Many sexually active women have HPV present at some time in their lives, and in most cases it disappears after a time with no resultant problems. It is the persistence of HPV, in particular a high risk type, that contributes to the development of cervical intraepithelial neoplasia and invasive cancer. Women with persistent HPV on smear tests are usually referred for colposcopy.[4]

Increase in cervical cancer with OC use for ≥ 5 years in HPV-positive women

A pooled analysis of eight case-control studies looking at the effect of oral contraceptives (OCs) on the risk of cervical cancer was published in March 2002 in the *Lancet*.[1] The International Agency for Research on Cancer (IARC) conducted the original studies in Spain, South America, Asia and Africa, between 1985 and 1997. The IARC analysis[1] looked only at women who were HPV-positive.

The results showed that women with HPV, who used oral contraceptives for less than five years, had no increase in risk of squamous-cell cervical cancer, compared to women with HPV who had never used OCs. In contrast, a duration of OC use of 5-9 years was associated with an almost three-fold increase in risk, compared with never-users, and a four-fold increase for usage of 10 years or longer. These estimates of risk were higher than those reported in most other studies.[2] Further research is needed to determine how long these risks persist after stopping OC use. The questionnaire used in the studies[1] did not specifically ask about type of hormonal contraceptive but from independent surveys and country usage data it is likely that the majority were taking a combined OC.

Analysis of only HPV-positive women reduces confounding

The IARC paper[1] eliminates a potential source of confounding present in earlier studies by analysing the effect of combined OC use in HPV-positive women. It was previously difficult to assess the influence of OC use on cervical cancer risk due to possible confounding by differences in sexual behaviour and HPV infection rates that may have been associated with use of OCs.

No association was found between presence of HPV and use of OCs among the controls.[1] This suggests that the increase in risk of cervical cancer from OCs is due to an effect on progression (from HPV infection to cancer), rather than affecting susceptibility or persistence of HPV infection.[2]

Regular cervical screening likely to offset increase in cancer risk

It is important to note that these case-control studies[1] were mostly in countries without a cervical screening programme. The Medicines Adverse Reactions Committee (MARC) has reviewed the IARC paper[1] and believes that the increase in cervical cancer risk in long-term users of OCs found in this study would be greatly reduced by the cervical screening programme in place in

New Zealand.[4] The MARC did not recommend that women with abnormal smears should stop taking OCs. The findings must be considered in light of the benefits of combined OCs (such as control of fertility and reduction in risk of uterine and ovarian cancer), and add further to our knowledge about the risks and benefits of hormonal contraception. The IARC paper[1] emphasises the importance of regular cervical screening in **all** women with a history of sexual activity, whether on OCs or not.

Competing interests (author): none declared.

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SAFETY ALERT: USE OF ALCOHOL BASED SKIN PREPARATIONS IN OPERATING THEATRES

On 15 October 2002, Medsafe issued an Urgent Safety Alert to hospitals regarding the use of alcohol based skin preparations in operating theatres. The Alert is to remind theatre staff of the potential flammability of alcohol based skin preparations and states that hospitals should review their policies and procedures on whether or not alcohol based skin preparations should be used in theatres. If alcohol skin preparations are used procedures must be in place to minimise danger to the patient.

This Safety Alert is available on the Medsafe website: www.medsafe.govt.nz/hot/alerts.htm

Following a recent operating room fire, detailed reports on this accident have been produced by both the Waitemata District Health Board and New Zealand Fire Service (available from www.medsafe.govt.nz/hot/alerts.htm and www.fire.org.nz/news/media.htm respectively).

The Royal Australasian College of Surgeons (RACS) New Zealand National Board is reviewing the use of alcohol based skin preparations in operating theatres. (The publications on operating room fires by the American College of Surgeons and on infection control by the Royal Australasian College of Surgeons should be noted: www.facs.org/about/committees/cpc/oper0897.html and www.racs.edu.au/wedo/publications/infection15.html)

Until the review by RACS is completed, if an alcohol based skin preparation is used the following measures are recommended:

1. The quantity of flammable fluid used to prepare the skin should be kept to a minimum in order to avoid run-off and pooling either on or around the patient. The amount of fluid in the bowl handed to the surgeon should be restricted and generally less than 100 ml.
2. The size of sponge applicators used for painting the skin should be reviewed. Some sponges can absorb up to 250–300 ml. Use of this volume will almost certainly lead to run-off.
3. Any run-off that occurs should be contained by absorbent material placed around the patient, which is removed before the drapes are applied.
4. Time should be allowed for the alcohol to evaporate and disperse prior to applying the drapes.
5. The addition of coloured dye to the skin preparation may assist in reducing the amount used and hence reduce run off.

Other issues to consider include the use of fire retardant drapes, fire retardant patient gowns and a gel fire blanket as part of the operating theatre safety equipment.

ADVERSE REACTIONS OF CURRENT CONCERN

MARC Rx ADVICE

The Medicines Adverse Reactions Committee (MARC) first initiated the list of a*dverse reactions of current concern* in 1994, to bring 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.

Regular amendments to the list of reactions are made either in response to adverse events reported in New Zealand or international pharmacovigilance issues. **The MARC has now added severe agitation, severe restlessness/ akathisia, and/or increased suicidality with selective serotonin re-uptake inhibitors (SSRIs).**

Recent additions

Agitation, restlessness, akathisia and/or increased suicidality with SSRIs

The possibility of SSRIs* being associated with suicidal ideation and suicide remains an open question. However, as described in the article on page 37, the more common cause of suicidal tendency during treatment with an antidepressant is inadequate treatment of depression.

For fluoxetine, the CARM database holds eights reports of suicidal tendency, one of suicide and five of suicide attempt; for paroxetine there are three reports of suicide and two of suicide attempt. No cases of similar events have been reported with the other SSRIs, but the total number of reports of any adverse reactions with these medicines is much lower. The MARC has listed severe agitation, severe restlessness/akathisia, and/or increased suicidality with SSRIs as *adverse reactions of current concern*. The intention is to obtain further information to clarify whether there may be a causal association between SSRIs and suicidal tendencies in some, probably rare, cases.

* SSRIs currently available in New Zealand: citalopram, clomipramine (a tricyclic antidepressant with potent serotonergic activity), fluoxetine, fluvoxamine, paroxetine and sertraline.

Updates on listings

NSAIAs and serious soft tissue infection

This was first listed as an *adverse reaction of current concern* in November 2000 following publication of a study[1] showing an association between the use of non-steroidal anti-inflammatory agents (NSAIAs) in children with primary varicella (chicken pox) and the development of necrotising fasciitis (NF) and serious complications of this disorder.

CARM received nine reports of soft tissue infection associated with NSAIAs up to November 2000. These included three reports of NF, five of sepsis and one of cellulitis. Since listing serious soft tissue infection with NSAIAs as an *adverse reaction of current concern*, CARM has received three further reports (one each of cellulitis, sepsis and NF). One of the patients was diabetic and developed NF at the site of a burn. He had received diclofenac for symptoms due to the burn. He required cardiorespiratory support and several surgical interventions as a result of the NF. The second patient had an undiagnosed streptococcal septicaemia, possibly due to a muscle abscess, and died. He had experienced non-specific symptoms and pain, and been given diclofenac prior to his death. The patient with cellulitis had an ischiorectal abscess, and was taking piroxicam and methotrexate. Duration of NSAIA use was unknown in the first patient, less than 24 hours in the second, and 9 months in the third patient.

There have been many published case reports of NF and serious soft tissue infection occurring in patients taking NSAIAs. Two New Zealand case

series[2,3] have been published; one[2] showed that five out of seven consecutive patients admitted to hospital with NF had taken NSAIAs, while the other[3] showed that five out of 13 similar patients had taken these medicines. Diabetes, obesity and/or multiple co-morbidities were present in the majority of patients in the second study[3], and the authors concluded that the role of NSAIAs remained unclear.

There are plausible reasons why NSAIAs may increase the severity of streptococcal infections. They have an inhibitory effect on several biological responses to infection and may also mask the symptoms of early infection. A fuller discussion can be found in the February 2001 issue of *Prescriber Update*.[4]

The small number of reports received by CARM suggests that if NSAIAs do precipitate or worsen soft tissue infection, they do so only rarely. Caution should be exercised when considering the use of NSAIAs in soft tissue injuries at risk of infection, and they should not be given to children with chicken pox. This reaction will remain of current concern as it is still controversial, the disorders of interest are serious, and it may be possible to build a profile of susceptible patients.

Hormone replacement therapy and venous thromboembolism

Since the listing of hormone replacement therapy (HRT) and venous thromboembolism (VTE) in April 1999 as an *adverse reaction of current concern*, there have been 13 further reports of deep vein thrombosis and two of pulmonary embolism. There have been no deaths but one patient with a pulmonary embolism also had right heart failure. VTE has occurred with oestrogen-only preparations, combined continuous and combined sequential preparations, and with most of the major oestrogens and oestrogen/progestogen combinations used as HRT in New Zealand. Premarin™ (conjugated equine oestrogens), followed by the combined continuous preparation Kliogest™ (2mg 17-beta-oestradiol and 1mg norethisterone), have the greatest number of reports, but as yet total numbers are small and these figures probably reflect sales. While the relative risk of VTE is similar to that with the combined oral contraceptive, the absolute risk with HRT is likely to be greater as the likelihood of VTE increases with age.

The results of the recently published Women's Health Initiative[5] randomised controlled trial of 161,809 women found a 2-fold increase in risk of pulmonary embolism and deep vein thrombosis with use of conjugated equine oestrogens and medroxyprogesterone acetate, compared with women not using HRT. This represents a rate of 34 cases per 10,000 women each year compared with 16 for non-users.

Please report **all cases** of adverse reactions in the table overleaf (additions are in bold), to 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 or www.medsafe.govt.nz/Profs/adverse.htm

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Medicine/s	Adverse reactions of current concern	*Prescriber Update* reference
Atypical antipsychotics	hyperglycaemia	Vol.23(1), Apr 2002 & No.18, Jun 1999
Celecoxib	cardiovascular events	Vol.23(1), Apr 2002
Celecoxib-warfarin interaction	increase in INR / haemorrhage	No.22, Oct 2001
Complementary and alternative medicines*	all adverse reactions	Vol.23(2), July 2002 & No.13, Oct 1996
Diane 35™ and 35 ED™	venous thromboembolism	No.20, Feb 2001
Estelle 35™ and 35 ED™	venous thromboembolism	No.22, Oct 2001
Hormone replacement therapy	venous thromboembolism	No.16, Apr 1998
Nefazodone	hepatic reactions	No.19, Feb 2000
NSAIAs	serious soft-tissue infection	No.20, Feb 2001
Oral contraceptives	venous thromboembolism	No.17, Dec 1998, No.11, Feb 1996 & Vol.23(1), Apr 2002
Rofecoxib	cardiovascular events	Vol.23(1), Apr 2002
Rofecoxib-warfarin interaction	increase in INR / haemorrhage	No.22, Oct 2001
selective serotonin re-uptake inhibitors (SSRIs)	**severe agitation, severe restlessness/akathisia, and/or increased suicidality**	**This issue (see above)**

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

INTENSIVE MEDICINES MONITORING PROGRAMME

About the IMMP

The purpose of the Intensive Medicines Monitoring Programme (IMMP) is to identify previously unrecognised adverse reactions to new medicines. It also develops adverse reaction profiles for these medicines, as well as measuring incidence and characterising reactions of clinical concern. In addition, the IMMP is able to identify any high-risk groups amongst the patients being treated. The results of IMMP findings are used to enhance the safe use of medicines.

Which medicines are monitored?

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

The medicines currently being monitored are listed below (no changes since the July 2002 issue of Prescriber Update).

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 or www.medsafe.govt.nz/Profs/adverse.htm

Medicine	Proprietary name/s	Indications/Action
Celecoxib	Celebrex	COX-2 inhibitor (selective NSAIA)
Clozapine	Clozaril, Clopine	atypical antipsychotic
Entacapone	Comtan	Parkinson's disease – adjunctive treatment only
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)
Sibutramine	Reductil	centrally acting anorexiant
Tolcapone	Tasmar	Parkinson's disease – adjunctive treatment only
Zafirlukast	Accolate	anti-asthmatic / leukotriene inhibitor

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CARM
CENTRE FOR ADVERSE REACTIONS MONITORING

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

Reporting form for Adverse Reactions to Medicines, Vaccines and Devices and all Clinical Events for IMMP

PATIENT DETAILS

H1574

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

ALL MEDICINES IN USE – ASTERISK SUSPECT MEDICINE(S)

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

DESCRIPTION OF ADVERSE REACTION OR INCIDENT

Date of Onset: _____

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

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

OTHER FACTORS

Renal Disease ☐ Hepatic Disease ☐ Allergy ☐ Describe:

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

REPORTING DOCTOR/PHARMACIST/NURSE

Name:	Telephone:
Address:	Date:
Email address:	

Send completed form to CARM

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

ADVERSE REACTIONS REPORTING GUIDELINES

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

Report adverse reactions to:

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

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

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

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

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

If in doubt, report.

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/reporting.html or www.medsafe.govt.nz/profs/adverse.htm

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

Or fax it to: (03) 479 7150

Phone: (03) 479 7247

Email: carmnz@stonebow.otago.ac.nz

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

1. The list of adverse reactions of current concern is on page 46.
2. The list of medicines in the Intensive Medicines Monitoring Programme (IMMP) is on page 47.