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Internet version: <http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/currentproblems/currentproblems.htm>

Statins and Cytochrome P450 interactions

Simvastatin: Updated prescribing advice on use with other drugs and avoidance of grapefruit juice

Some statins (particularly simvastatin and atorvastatin) are metabolised by cytochrome P450 (CYP3A4) and co-administration of potent inhibitors of this enzyme (such as 'azole' anti-fungal agents or HIV protease inhibitors) may particularly increase plasma levels of these drugs and so increase the risk of dose-related side effects, including rhabdomyolysis.

The risk of serious myopathy is also increased when high doses of simvastatin are combined with less potent inhibitors of CYP3A4, including amiodarone, verapamil and diltiazem.

In addition, recent pharmacokinetic evidence suggests that grapefruit juice should be avoided altogether, as even modest quantities of this drink can significantly increase exposure to simvastatin¹.

A European-wide procedure to harmonise the nationally approved product information for simvastatin has been recently completed. The prescribing guidance for co-administering these drugs with simvastatin is summarised in the table on page 2.

Other statins

For atorvastatin, caution should be exercised when combining with any CYP3A4 inhibitor, especially at high doses, and patients should also avoid drinking large quantities of grapefruit juice. Fluvastatin is metabolised by a different cytochrome P450 enzyme (CYP2C9), whilst pravastatin and rosuvastatin[▼] are not substantially metabolised by cytochrome P450.

Warfarin

Care is needed when prescribing some statins to patients taking warfarin – please check the specific product information for further advice on possible interactions.

Always consider possible interactions when prescribing statins

Updated prescribing advice for simvastatin

Interacting drug	Prescribing advice
Potent CYP3A4 inhibitors: HIV protease inhibitors Azole antifungal agents Erythromycin, Clarithromycin, Telithromycin	Avoid simvastatin
Cyclosporin, gemfibrozil, niacin (>1 g/day)	Do not exceed 10 mg simvastatin
Verapamil, amiodarone	Do not exceed 20mg simvastatin
Diltiazem	Do not exceed 40mg simvastatin
Grapefruit juice	Avoid grapefruit juice when taking simvastatin

Rosuvastatin▼

Always start at 10mg, specialist advice recommended for titration to 40mg

Rosuvastatin▼ is a potent HMG Co-A reductase inhibitor that was licensed and launched in the UK in March 2003. As with other statins, muscle toxicity is a recognised, dose-related adverse reaction, leading in rare cases to rhabdomyolysis. The CSM has received 10 reports of suspected rhabdomyolysis with rosuvastatin▼. In a number of cases, the reports have involved patients who have started on high doses of rosuvastatin▼ and some have had pre-existing risk factors for myopathy. The Marketing Authorisation holder for rosuvastatin▼ has recently distributed two letters to UK prescribers.

The main points are:

- All patients must start on the initial dose of **10mg rosuvastatin▼ once daily** and should only be titrated to 20mg if considered necessary after a 4-week trial of 10 mg.
- The **40mg dose** is contraindicated in patients with predisposing risk factors for muscle toxicity.
- Specialist supervision is recommended when the 40mg dose is initiated (through local lipid, diabetic or cardiac clinics). The 40mg dose should only be necessary for the minority of patients with severe hypercholesterolaemia at high cardiovascular risk.

Patients who are currently taking 40mg and who have not already been seen by a specialist should have their

treatment reviewed at their next routine appointment and appropriate down-titration of dose or specialist referral should be considered.

Update on statins and rhabdomyolysis

Evidence from a variety of long-term studies of HMG CoA reductase inhibitors (statins - particularly simvastatin^{2,3} and pravastatin^{4,5,6}) has demonstrated that these products are highly effective in reducing morbidity and mortality from coronary artery disease. The most common adverse reactions of statins are relatively non-serious and transient. Rare but clinically important adverse effects are elevations in hepatic transaminases, peripheral neuropathy, and myopathy including rhabdomyolysis (which is potentially life-threatening).

The exact mechanism by which statins cause rhabdomyolysis remains unclear, but the risk appears to be dose-related. Risk factors include:

- Underlying muscle disorders, renal impairment, untreated hypothyroidism, alcohol abuse and age >70 years.
- Concomitant use of other lipid lowering agents i.e. gemfibrozil, fenofibrate, other fibrates or nicotinic acid.
- A history of myopathy with any lipid-lowering treatment.
- Interactions (e.g. with drugs inhibiting cytochrome P450 – see table above).

Prescribers are reminded of the need to adjust doses of statins in accordance with the recommendations of each Summary of Product Characteristics.

Patients receiving any statin should be asked to report muscle pain, weakness or cramps immediately, and stop treatment until this has been investigated. If symptoms are severe or if creatine kinase is greater than 5 times the upper limit of normal, treatment should be withheld.

Please report all suspected adverse drug reactions with rosuvastatin▼ and any serious suspected reactions with simvastatin, fluvastatin, atorvastatin and pravastatin.

- 1 Lilja J J et al. Brit J Clin Pharmacol 2004; 58: 56-59.
- 2 Scandinavian Simvastatin Survival Group. Lancet 1994; 344: 1383-1389.
- 3 Heart Protection Collaborative Group. Lancet 2002; 360:7-22.
- 4 Sacks FM et al. N Eng J Med 1996; 335: 1001-1009.
- 5 Shepherd J et al. N Eng J Med 1995; 333: 1301-1307.
- 6 LIPID study group. N Eng J Med 1998; 339: 1349-1357.



Reminder: Paroxetine prescribing advice

The recommended adult daily dose is **20mg** for the treatment of depression, social anxiety disorder (SAD), generalised anxiety disorder (GAD) and post traumatic stress disorder (PTSD), and **40mg** for the treatment of obsessive compulsive disorder (OCD) and panic disorder. Evidence from clinical trials of additional efficacy above the recommended dose is lacking¹.

Paroxetine should not be used in patients under 18 years in the treatment of depressive illness because of an increased risk of a number of adverse effects including suicidal thoughts and self harm, and a lack of efficacy in this population².

The available data do not suggest an increased risk of suicidal behaviour in adults aged 18 or over, however, an increased risk in some young adults cannot be ruled out. **Young adults treated with paroxetine should be carefully monitored throughout treatment**³.

As with all antidepressants, the risk of suicidal behaviour may increase at the beginning of treatment⁴.
⁵. Patients should be reviewed every 1-2 weeks at the start of antidepressant treatment⁶.

Due to the **risk of withdrawal reactions**, patients taking paroxetine should not stop the drug suddenly. Cessation of treatment should involve a very gradual downward titration. If intolerable symptoms develop it may be necessary to reinstate the previously prescribed dose and withdraw more gradually⁷.

1. Public Health Link message of 11 March 2004 from Chairman of CSM.
2. Public Health Link message of 10 June 2003 from Chairman of CSM.
3. MHRA and CPMP websites information issued on 22 April 2004.
4. Jick H, Kaye JA, Jick SS. JAMA 2004; 292: 338-343.
5. MCA/CSM Current Problems in Pharmacovigilance 2000; 26: 3-4.
6. British National Formulary, 47, section 4.3.
7. MHRA/CSM Current Problems in Pharmacovigilance 2003: 29: 4.

Cisapride: licences cancelled

The UK Marketing Authorisations (MA) for cisapride-containing products were suspended in July 2000, following advice from the CSM, due to the risk of cardiac side effects. CSM advised that the balance of risks and benefits was no longer favourable.

This advice was communicated to UK health professionals¹. Following this suspension, a Europe-wide review of the

risks and benefits of cisapride took place under the auspices of the Committee for Proprietary Medicinal Products (CPMP).

On the advice of the CPMP, the European Commission decided that cisapride-containing products should be maintained within Europe but with restricted indications in adults and children after failure of other treatment options. A condition of the MAs was that all patients treated with cisapride should be enrolled in either a clinical safety study/registry or a clinical trial to evaluate efficacy.

The UK MAs remained suspended until October 2003, when the MA Holder, Janssen Cilag, voluntarily decided not to implement the EU decision in the UK. Instead they have decided to cancel all existing UK MAs.

1. MCA/CSM Current Problems in Pharmacovigilance 2000; 26: 9.

Tolcapone (Tasmar[▼]): return to market

Tolcapone (Tasmar[▼]) is a catechol-O-methyltransferase (COMT) inhibitor medicine developed for use in Parkinson's disease. In February 1999 we informed you of the withdrawal of tolcapone following serious hepatic reactions and neuroleptic malignant syndrome (NMS)¹.

At its April 2004 meeting the European Committee for Proprietary Medicinal Products recommended lifting the suspension of the Marketing Authorisation for tolcapone. This followed review of the available clinical evidence including evidence of increased efficacy for tolcapone over entacapone in the control of motor fluctuations in patients with advanced Parkinson's disease.

Tolcapone will be made available with the restricted indication in patients "who failed to respond to or are intolerant of other COMT inhibitors".

The following conditions will be applied to use of Tasmar:

- More frequent liver function monitoring and closer attention to the monitoring of possible signs and symptoms of underlying liver disease.
- Contraindication in patients with severe dyskinesia or with a previous history of NMS.
- Restriction on prescribing to physicians experienced in the management of advanced Parkinson's disease.

The safety of Tasmar[▼] will be closely monitored by the MHRA and CSM.

1. MCA/CSM Current Problems in Pharmacovigilance 1999; 25: 2.

Review of the evidence on long-term safety of HRT

In the last 2 years several important studies of the use of hormone replacement therapy (HRT) have been published, including the Women's Health Initiative (WHI) randomised placebo-controlled trial and the large observational Million Women's Study (MWS) in the UK.

Previous editions of *Current Problems in Pharmacovigilance*^{1, 2} have described the implications of the findings from these studies for prescribing HRT in the UK. In December 2003, the Chairman of the Committee on Safety of Medicines (CSM) wrote to all health care professionals advising them that for the prevention of osteoporosis, the risks from long-term use of HRT outweighed the benefits and that, in women over the age of 50, HRT should no longer be the therapy of first choice for this purpose.

Since then, the oestrogen-only HRT arm of the WHI trial³ and the *HABITS* trial⁴ have been stopped early (see below). This article summarises the current evidence on the long-term safety of HRT and presents the latest advice from the CSM.

New data

WHI trial - Oestrogen-only HRT

In March 2004, the oestrogen-only (conjugated equine oestrogen, 625micrograms daily) arm of the WHI trial, in women aged between 50 and 79 years and with a hysterectomy, was stopped after 6.8 years, a year ahead of schedule⁴.

This decision was to avoid the unnecessary exposure of women to an increase in the risk of stroke in view of the anticipated lack of change in outcome for breast cancer (which was not increased in users) or for heart disease (which showed no benefit).

WHI Memory Study (WHIMS)

The oestrogen-only arm of a sub-study of the WHI trial, WHIMS, was stopped at the same time as the main study. WHIMS investigated the effect of conjugated equine oestrogen (625micrograms daily) on the development of dementia, prevention of mild cognitive impairment and global cognitive function.

The results of this study^{5, 6} indicate that conjugated equine oestrogen does not protect women over the age of 65 years against mild cognitive impairment or probable dementia.

MWS - Mammography

New data on the adverse effect of HRT on mammography have become available from the large UK observational study of women attending for the NHS breast screening programme, the Million Women Study^{7, 8}.

HABITS trial

In February 2004, this randomised, prospective follow-up study, which examined the risk of breast cancer recurrence with HRT use, was prematurely stopped. In this study even short-term use of HRT was found to pose an unacceptably high risk of disease recurrence in women who had previously had breast cancer. A similar trial, the Stockholm study, did not find such an increase but was also stopped, primarily on the grounds that recruitment would now be overwhelmingly difficult³.

Further data from the oestrogen-only arm of the WHI trial and the MWS are expected.

Benefits of HRT

Menopausal symptoms

HRT is effective in relieving symptoms of the menopause. These may include hot flushes, night sweats, vaginal dryness and discomfort, difficulty in sleeping and consequential depression, mood swings, tiredness and poor concentration. In most cases, the short-term use of HRT is enough to relieve these symptoms, which may recur for a short time after stopping therapy.

Osteoporosis

Use of oestrogen-only and combined HRT can help prevent osteoporosis (thinning of the bones) and so reduce the risk of hip (see table on page 6) and other fractures⁹. These beneficial effects do not persist for long after HRT is stopped.

Colon cancer

In the WHI trial, combined HRT, but not oestrogen-only HRT, significantly reduced the number of cases of colon cancer (see table on page 6).

Risks of HRT

The main risks associated with HRT are summarised below - where possible, estimates of absolute risk are provided in the table on page 7. CSM advice remains that for the majority of women with menopausal symptoms that affect their quality of life the risk is generally small and is outweighed by the benefits of short-term treatment. Women should be counselled appropriately with respect to the benefits and possible risks (see table on page 6).

Much of the evidence from randomised controlled trials relates to the specific use of oral conjugated equine oestrogen with or without added medroxyprogesterone acetate. It is not yet clear whether these risks extend to all other HRT products, however, the limited available data do not suggest substantial variation between products.

Breast cancer

The Million Women Study¹⁰ (MWS) demonstrated an association between HRT and an increased risk of invasive breast cancer that increased with duration of use.

The risk of breast cancer is increased within a few years of starting HRT but falls when women stop treatment, reaching the same level as women who have never taken HRT within 5 years of stopping.

The relative risk of breast cancer was significantly greater for combined HRT (relative risk, RR = 2.00 [1.88-2.12] versus non HRT-users) than for oestrogen-only HRT (RR=1.30 [1.21-1.40] versus non HRT-users) and was the same for all combined products, irrespective of the type of progestogen and its sequential or continuous addition to oestrogen.

The combined arm of the WHI trial (conjugated equine oestrogen, 625micrograms daily and medroxyprogesterone acetate, 2.5mg daily)¹¹ demonstrated a significant increase in the risk of breast cancer that increased with duration of treatment (RR = 1.24 [1.02-1.54] versus placebo).

Preliminary results from the oestrogen-only arm of this trial⁴ in women with a hysterectomy, demonstrated no increase in the risk of breast cancer after an average of 6.8 years of treatment (RR = 0.77 [0.59-1.01] versus placebo)¹.

The relative risks observed in association with both the combined and oestrogen-only HRT preparations in the WHI trial are lower than those seen in the MWS and other observational studies.

New data from the MWS confirm that HRT adversely affects the sensitivity and specificity of mammography and therefore the radiological detection of breast cancer. They also suggest that the effect of HRT on mammographic specificity may last for up to 5 years after stopping treatment. *CSM has advised that stopping HRT in the weeks prior to mammography may therefore be of no benefit.*

Recent evidence from the HABITS trial suggests that HRT may increase the recurrence of breast cancer in

women who have previously had the disease. However, a similar study in Stockholm showed no increase and data from further trials are awaited. HRT is contraindicated in women who have previously had breast cancer.

Coronary heart disease (CHD)

The combined arm of the WHI trial (in mainly healthy women) and the Heart and Estrogen/progestin Replacement Study (HERS, in women with a history of heart disease) have both shown a possible small increase in the risk of coronary heart disease in the first year of using conjugated equine oestrogen and medroxyprogesterone acetate and no evidence of overall benefit in up to 5 years' use. The oestrogen-only arm of the WHI trial also failed to show cardioprotection.

Stroke

The WHI trial found an increase in the risk of stroke in HRT users that was of similar magnitude in both the combined HRT and oestrogen-only HRT arms.

Cognitive function

In the WHIMS study, in women who started HRT after the age of 65 years, conjugated equine oestrogen did not protect against mild cognitive impairment or probable dementia.

Furthermore, in the combined arm of this study, conjugated equine oestrogen and medroxyprogesterone acetate doubled the risk of probable dementia, an effect that was only significant in women over the age of 75 years. These findings may be of little relevance to HRT users in the UK, the majority of whom use HRT at a much earlier age.

Venous thromboembolism

HRT has been shown to increase the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in the vast majority of studies, an effect that is greatest in the first year of using HRT.

Endometrial cancer

In women with an intact uterus the risk of endometrial hyperplasia and cancer increases with increasing dose and duration of use of unopposed oestrogens. Adding a progestogen to oestrogen-only therapy for at least 12 days per month greatly reduces this risk.

Ovarian cancer

Observational studies¹²⁻¹⁴ indicate a small increase in the risk of ovarian cancer in hysterectomised women after long-term oestrogen-only HRT. The risks associated with use of combined HRT are currently unknown.

Summary of the risks and benefits associated with using HRT.

Condition	Age of woman (yr)	Number of cases/ 1000 non-HRT users		Extra number of cases in 1000 HRT users for 5 years HRT use over the same period*	
Cumulative cancer risk over 5 years				Oestrogen-only	Combined HRT
Breast cancer Million Women Study	50-64	14 ^a		1.5 (±1.5)	6 (±1)
		CEE ^b	CEE + MPA ^b		
WHI	50-79	15	16	No significant effect	4 (±4)
Endometrial cancer	50-69	3 ^b		5 (±1) ^c	Cannot be estimated ^d
Ovarian cancer^e	50-69	3		1 (±1)	Not known
Cardiovascular risks over 5 years					
		CEE ^b	CEE + MPA ^b		
Stroke	50-59	8	3	2 (±2)	1 (±1)
	60-69	15	11	6 (±4)	4 (±3)
VTE	50-59	6.5	3	1 (±1)	4 (±2)
	60-69	11.5	8	4 (±4)	9 (±5)
Benefits over 5 years				Reduced number of cases in 1000 HRT users over the same period	
		CEE ^b	CEE + MPA ^b		
Colorectal cancer	50-59	6	3	No significant effect	1 (±1)
	60-69	10	8		3 (±2)
Fracture of neck of femur⁹	50-59	0.5	1.5	0.3 (±0.5)	0.3 (±1)
	60-69	5.5	5.5	3 (±2)	3 (±2)

Numbers are best estimates (± approximate range from 95% Confidence Intervals).

* All values are from the WHI trial unless otherwise stated.

^a A cumulative risk of 14 cases/1000 non-HRT users over 5 years has been used to facilitate comparison of the MWS and the WHI studies.

^b Estimates from the placebo groups of the WHI trial.

^c Relative risk associated with 5 years' use of oestrogen-only HRT (RR = 2.8[2.3-3.5] from meta-analysis¹⁵).

^d Risk cannot be reliably estimated - the addition of a progestogen for at least 12 days per month greatly reduces the additional risk of endometrial cancer due to unopposed oestrogen, but the magnitude of the reduction is poorly defined at present.

^e Sources of data for all ovarian cancer estimate ^{12, 13, 14}.

1. MCA/CSM Current Problems in Pharmacovigilance. 2002; 28: 1-2.
2. MHRA/CSM Current Problems in Pharmacovigilance. 2003; 29: 1-3.
3. Holmberg L and Anderson H for the HABITS Steering and Data Monitoring Committees. Lancet 2004;363:453-455.
4. Women's Health Initiative Steering Committee. JAMA 2004; 291: 1701-1712.
5. Schumaker S et al for the Women's Health Initiative Memory Study Investigators. JAMA 2004; 291: 2947-58.
6. Espeland M et al. for the Women's Health Initiative Memory Study Investigators. JAMA 2004; 291: 2959-68.
7. V Beral et al., Menopause and Hormone Replacement, RCOG Press 2004 (in press).
8. E Banks et al., BMJ 2004; 328: 1291-2.
9. Cauley JA et al., JAMA 2003; 290(13): 1729-38.
10. Million Women Study Steering Committee Lancet 2003; 362: 419-427.
11. Writing Group for the Women's Health Initiative Investigators. JAMA 2002; 288(3): 321-222.
12. Lacey JV, et al.. JAMA 2002; 288(3): 334-342.
13. Riman et al., J Natl Cancer Inst 2002; 94: 497-504.
14. Rodriguez et al., JAMA 2001; 285: 1460-1465.
15. Grady D et al., Obstet & Gynaecol. 1995; 85: 304-313.

HRT advice for prescribers

- For the treatment of menopausal symptoms the benefits of short-term HRT are considered to outweigh the risks in the majority of women.
- Each decision to start HRT should be made on an individual basis with a fully informed woman.
- In all cases, it is good practice to use the lowest effective dose for the shortest possible time and to review the need to continue treatment at least annually. This review should take into account new knowledge and any changes in a woman's risk factors and personal preferences.
- For postmenopausal women who are at an increased risk of fracture and are aged over 50 years, HRT should be used to prevent osteoporosis only in those who are intolerant of, or contraindicated for, other osteoporosis therapies.
- Women who are receiving HRT for their menopausal symptoms will benefit from the effect of HRT on osteoporosis prevention whilst on treatment.
- Healthy women who have no menopausal symptoms should be advised against taking HRT as the risks outweigh the benefits.
- HRT does not prevent coronary heart disease or a decline in cognitive function and should not be prescribed for these purposes.
- HRT remains contraindicated in women who have had breast cancer.
- For women without a uterus, oestrogen-only therapy is appropriate.
- For women with a uterus, oestrogen plus progestogen is recommended. However, women should be fully informed of the added risk of breast cancer and be involved in the decision-making process.

Combined oral contraceptives: Venous thromboembolism

Yasmin and the risk of venous thromboembolism - comparable with other combined oral contraceptives

Venous thromboembolism (VTE) is a very rare reaction that is well known to occur in association with combined (oestrogen and progestogen) oral contraceptives (COCs). There is evidence to suggest that the level of risk of VTE differs depending on which progestogen is used in the pill. Yasmin is the first combined contraceptive to contain the progestogen drospirenone. In addition to its progestogenic action, drospirenone has antiandrogenic and mild antimineralocorticoid properties. Since VTE is a rare event, the exact risk of VTE associated with the combination of drospirenone with oestrogen in Yasmin was not known at the time of licensing. This lack of data is reflected in product information.

Data from a Prescription Event Monitoring study carried out in the UK suggested that there might be a high rate of VTE associated with Yasmin. However, this is a non-comparative study in which women were evaluated in their first year of using Yasmin, when the risk of VTE in association with any COC is known to be highest. Reassuringly, interim data from a large, non-interventional, comparative cohort study (Yasmin users, levonorgestrel COC users and other COC users), that has so far examined over 52,000 women-years (approximately 46,500 women) of exposure, including over 16,000 women-years in

Yasmin, suggest that the rate of VTE in Yasmin users is comparable with the rate in users of the comparator combined oral contraceptives. This study will be finalised in early 2006 and the results will be available mid 2006.

In contrast to previous observational studies, which had very strict exclusion criteria, women with additional risk factors for VTE (such as obesity, surgery and immobility) were included in both these studies. Reported incidences of VTE are therefore higher than those currently quoted in product information.

Prescribers are reminded that:

- All combined oral contraceptives increase the risk of VTE.
- In a large cohort study the risk of VTE associated with use of Yasmin does not appear to differ from that associated with use of the comparator combined oral contraceptives.
- Many factors increase the risk of VTE, including obesity (BMI>30), and these should be taken into consideration when deciding which is the most suitable method of contraception.

Prescribing note:

Combined oral contraceptives, including Yasmin, should be prescribed with caution to obese women (BMI>30), or those with a higher baseline risk of VTE.



Reminder: Thiazolidinediones (glitazones) contraindications

Rosiglitazone and pioglitazone are contraindicated in combination with insulin and in patients with cardiac failure or a history of cardiac failure

Evidence from Yellow Cards and usage data indicate that rosiglitazone and pioglitazone are being prescribed in combination with insulin, despite this being a contraindication for both products.

These data also indicate that thiazolidinediones are being prescribed in patients with cardiac failure, which is a contraindication with rosiglitazone and pioglitazone. This off-label use of glitazones may be causing or aggravating cardiac failure.

Diabetes is in itself a strong risk factor for congestive heart failure (CHF)¹. Since 2000, approximately 120,000 patients have received a prescription for rosiglitazone and 33,000 patients for pioglitazone in the UK².

Seven spontaneous reports of cardiac failure or oedema or both in patients receiving either rosiglitazone or pioglitazone in combination with insulin have been received. In addition 12 reports of aggravated cardiac failure in association with the use of these agents have been received. Due to higher levels of patient exposure, rosiglitazone has been associated with the greatest number of spontaneous reports.

Prescribers are reminded that rosiglitazone and pioglitazone should not be used:

- In patients with cardiac failure or a history of cardiac failure (NYHA stages I to IV).
- In combination with insulin.

1. Nesto R.W. Circulation 2003; December 9: 2941-2948.
2. DIN-LINK, CompuFile Ltd, May 2004.

Risk: benefit of Co-proxamol

In England and Wales between 300 and 400 people die each year following deliberate or accidental overdose with co-proxamol (Distalgesic; Cosalgesic; Dolgesic), a fixed-dose combination of paracetamol (325mg) and the weak opioid analgesic, dextropropoxyphene (32.5mg) indicated for the treatment of mild to moderate pain.

Combination with alcohol or CNS depressants is

particularly hazardous and may cause fatal apnoea or cardiac arrhythmia. The rationale for the extensive use of this combination product is not evidence based; dextropropoxyphene is a weak analgesic and co-proxamol has not been shown to have greater efficacy than full strength paracetamol. In view of its well-established toxicity in overdose and poorly defined clinical value, the role of co-proxamol is currently under review and is the subject of a public request for information (consultation details are available on the MHRA website www.mhra.gov.uk).

In order to reduce the risk of fatal self-poisoning with co-proxamol, prescribers are reminded to:

- **RESTRICT** the number of tablets prescribed at any one time to the smallest quantity necessary for the condition being treated.
- **AVOID** prescribing co-proxamol for patients who may be at risk of self-poisoning or those with a history of alcohol abuse.
- **ADVISE** patients that the tablets are for their use only; the recommended dose must not be exceeded; that the drug can be extremely dangerous if taken with alcohol or CNS depressants and that unwanted tablets should be returned to a pharmacy for disposal.
- **INFORM** patients that they should be given a patient information leaflet with their medicine and to ask for one if it is not offered.

SSI BCG vaccine and local reactions

Statens Serum Institut (SSI) BCG vaccine was introduced into the UK immunisation schedule in November 2002 following withdrawal of the Evans BCG vaccines.

There are 2 important differences between the Evans and SSI products. Firstly, SSI BCG is available only as an intradermal formulation and this technique has replaced use of the percutaneous technique in younger children. Secondly, the lower age limit for use of the 0.1ml dose of vaccine has increased from 3 months to 1 year. There are other pharmaceutical differences between the Evans and SSI BCG vaccines. In particular, SSI vaccine contains a more potent substrain¹ of *Mycobacterium bovis*, compared with the previous Evans vaccine.

The MHRA and CSM have recently reviewed the suspected adverse drug reactions (ADRs) reported via the Yellow Card Scheme in association with SSI BCG in the context of those reported in association with

Evans BCG vaccine over the preceding 10 years. The most commonly reported ADRs were similar for both vaccines. Almost half of the suspected ADRs received in association with the SSI BCG vaccine to date have been due to immediate reactions such as fainting that are most likely to result from reactions to the process of vaccination rather than the vaccine itself. This is not uncommon when vaccines are administered to adolescents.

Injection site reactions contribute almost a quarter of all ADRs reported with SSI BCG vaccine, the majority of which were not serious. CSM noted that a higher proportion of local reactions associated with SSI BCG vaccine have been reported in neonates and young children compared to BCG vaccine in the preceding 10 years.

It is not clear whether this increase in reporting of injection site reactions in these age groups compared to Evans vaccine is a consequence of an increase in immunisation of neonates and infants, a more reactogenic vaccine, a more difficult injection technique, or a combination of these factors.

As expected for a new black triangle drug, the reporting rate for ADRs with SSI BCG is higher than for the old Evans vaccine, but the true incidence of ADRs cannot be calculated on the basis of Yellow Card data. The CSMs recent review has not identified any new safety concerns for SSI BCG. The product information for SSI BCG gives detailed guidance on the intradermal administration technique and this should be adhered to.

As with all medicines and vaccines, the MHRA and CSM will continue to keep the safety of SSI BCG vaccine under review. Please report suspected adverse reactions associated with vaccines through the Yellow Card Scheme.

1. Smith & Starke (1999). Bacille Calmette-Guerin Vaccine. In Plotkin S & Orenstein W, eds. *Vaccines* Philadelphia, Pennsylvania, WB Saunders Company, 1999: 111-139.

Changes in the names of certain medicines

Confusion between Mercaptamine and Mercaptopurine

Mercaptamine is the new name for Cysteamine following the recent changeover from British Approved Names (BANs) to recommended International Non-Proprietary Names (rINNs). On 8 June 2004, we sent a message to healthcare professionals asking them to take particular care when prescribing or dispensing

mercaptamine and mercaptopurine.

A number of incidents have been reported to the MHRA involving confusion between mercaptamine and mercaptopurine due to the similarity in their names and the fact that both are available as 50mg solid oral dose presentations.

Further information, including the full text of the message and advice from the National Patient Safety Agency on how to minimise the risk of medication errors during the BANs to rINNs changeover can be found on the MHRA website at <http://medicines.mhra.gov.uk/inforesources/productinfo/banrinn.htm>

Pharmacists are asked to be particularly vigilant when dispensing these medicines.



Reminder: Flucloxacillin and serious hepatic disorders

Flucloxacillin treatment is very rarely associated with an increased risk of hepatic disorders, namely, hepatitis and cholestatic jaundice. In some patients, almost always those with serious underlying disease, these adverse reactions have been fatal.

The Committee on Safety of Medicines (CSM) has previously advised that:

- The onset of hepatic reactions may be delayed for several weeks (up to 2 months) after treatment with flucloxacillin has stopped.
- These reactions are related neither to the dose nor to the route of administration of flucloxacillin.
- Risk factors include treatment for more than 2 weeks and increasing age.

Prescribers are reminded that:

- Flucloxacillin should not be used in patients with a history of flucloxacillin-associated jaundice or hepatic dysfunction.
- Flucloxacillin should be used with caution in patients with evidence of hepatic dysfunction.
- Careful enquiry should be made concerning previous hypersensitivity reactions to β -lactams.

1. MCA/CSM Current Problems 1992; 35: 2.

Interaction between warfarin and cranberry juice: new advice

Patients taking warfarin should avoid taking cranberry juice, or other cranberry products unless the health benefits are considered to outweigh any risks

Last year two publications relating to Yellow Card reports highlighted a possible interaction between warfarin and cranberry juice^{1,2}. In addition, a further case report has been published this year³.

Following this publicity, we have now received a total of 12 reports of suspected interactions involving warfarin and cranberry juice. Eight cases involved increases in INR and/or bleeding episodes, in three cases the INR was reported to be unstable and in one case the INR was seen to decrease.

CSM has reviewed these cases and concluded that there is now sufficient evidence of an interaction for formal advice to be issued.

It is not possible to define a safe quantity or brand of cranberry juice, therefore patients taking warfarin should be advised to avoid this drink unless the health benefits are considered to outweigh any risks. Increased medical supervision and INR monitoring should be considered for any patient taking warfarin and a regular intake of cranberry juice.

It is not known whether other cranberry products, such as capsules or concentrates, might also interact with warfarin. Therefore similar caution should be observed with these products.

Product information for warfarin products is in the process of being updated to reflect this new advice.

1. MHRA/CSM Current Problems in Pharmacovigilance. 2003; 29: 8.
2. R Suvarna et al. BMJ 2003; 327: 1454.
3. P Grant. The Journal of Heart Valve Disease 2004; 13: 25-26.

Black cohosh (*cimicifuga racemosa*) and hepatotoxicity

Hepatotoxicity has been reported with black cohosh

Black cohosh (*cimicifuga racemosa*) has traditionally been used to treat a variety of conditions including rheumatism, rheumatoid arthritis, intercostal myalgia, sciatica, chorea, tinnitus, dysmenorrhoea, and uterine colic. Currently black cohosh is mainly used to treat

menopausal symptoms and it may become more widely used as women seek an alternative to hormone replacement therapy. However, the efficacy and long term safety of black cohosh is not clear.

Recognised adverse effects of black cohosh include gastrointestinal irritation, headache, dizziness and vomiting.

There have been 10 reports of suspected adverse reactions associated with black cohosh, 7 of which have been reports of hepatotoxicity. The first case of hepatotoxicity was reported in 1998.

One of the seven cases involved a woman who developed life-threatening hepatitis with cholestatic jaundice. No medical cause was identified and the patient was on no other medication. In another case a woman developed hepatitis and investigations to exclude other causes of hepatitis were negative. The remaining 5 cases had abnormal liver function tests. All patients recovered or were recovering at the time of reporting.

Outside the UK, two cases have been reported where the patients have required liver transplantation; one was associated with a herbal remedy containing several other ingredients^{1,2}.

The mechanism for hepatotoxicity with black cohosh is not known. However, an immunological response has been suggested¹.

Healthcare professionals are reminded to ask about the use of herbal medicines in patients presenting with symptoms or signs of hepatotoxicity and to report, via the Yellow Card Scheme, cases of hepatotoxicity or any other suspected adverse reactions associated with black cohosh.

1. Whiting PW et al. MJA 2002; 177: 440-443.
2. Lontos S et al. MJA 2002; 390-39.



Reminder: Safety of Traditional Chinese Medicines and herbal remedies

Healthcare professionals are reminded to ask patients about their use of herbal remedies and Traditional Chinese Medicines when investigating possible adverse reactions. The MHRA continues to receive reports of Traditional Chinese Medicines (TCM) containing prohibited ingredients. Examples of ingredients we have identified in TCMs include the following:

Prohibited herbal ingredients:

- **Aristolochia**: prohibited in unlicensed medicines. It is associated with kidney failure and cancer.
- **Ephedrine**: not permitted to be added to unlicensed herbal medicine. It has been associated with cardiac problems and stroke.

Prescription medicines:

- **Corticosteroids**: have been found in “herbal” creams used to treat skin conditions. Particularly where used in uncontrolled amounts, topical corticosteroids may cause skin thinning and in the long term worsen conditions such as eczema and dermatitis as well as local, and possibly systemic, immunosuppression.
- **Fenfluramine**: an appetite suppressant which was associated with cardiac problems and withdrawn globally on safety grounds. **Nitrosofenfluramine**, a related substance, is toxic to the liver.
- **Glibenclamide**: an anti-diabetic agent. Improper use can result in coma and death.

Toxic and biological products:

- **Mercury, lead and arsenic**: not permitted in unlicensed herbal medicines. These variously can cause harmful effects including severe nausea, abdominal pain, kidney damage, impairment of mental function and convulsions.
- **Human placenta**: not permitted in unlicensed herbal medicines. Possible risk of transferring infections such as hepatitis C or HIV.
- **Excreta from bats**: animal ingredient not permitted in unlicensed herbal medicines. May pose a variety of public health risks.

The presence of these substances is illegal and potentially very harmful. The patient may not be aware of the added ingredient as these ingredients are usually not declared on the product label.

Please report any suspected adverse reaction associated with herbal remedies or Traditional Chinese Medicines through the Yellow Card Scheme.

1. MCA/CSM Current Problems in Pharmacovigilance 1999; 25: 18.
2. MCA/CSM Current Problems in Pharmacovigilance 1996; 22: 10.
3. MCA/CSM Current Problems in Pharmacovigilance 2001; 27: 12.
4. MCA/CSM Current Problems in Pharmacovigilance 2002; 28: 6.

Dose adjustment and monitoring of Low Molecular Weight Heparins

New advice for enoxaparin (Clexane): patients with severe renal impairment

Monitoring Anti Factor-Xa activity may be helpful in patients receiving LMWH who are at risk of bleeding or are actively bleeding

Bemiparin, certoparin, dalteparin, enoxaparin, reviparin and tinzaparin are Low Molecular Weight Heparins (LMWHs), licensed for differing indications. LMWHs are indicated for the prevention of venous thromboembolism and some are also indicated for the treatment of deep venous thrombosis, pulmonary embolism, unstable coronary artery disease and for the prevention of clotting in extracorporeal circuits.

Prescribers are reminded of the need to refer to individual product information regarding indications, cautions, appropriate dose-adjustment and contraindications in patients with risk factors for bleeding, such as renal or hepatic impairment.

Severe renal impairment is a contraindication for use of reviparin and certoparin, whereas caution is advised for dalteparin and bemiparin and dose reduction should be considered for tinzaparin.

The Marketing Authorisation holder for enoxaparin has issued new prescribing advice on dose reduction in severe renal failure and this is summarised below. Careful clinical monitoring is advised for mild/moderate renal impairment.

Enoxaparin: New prescribing advice

Treatment dosage ranges

Standard dosing	Severe renal impairment
1 mg/kg twice daily	➡ 1 mg/kg once daily
1.5 mg/kg once daily	➡ 1 mg/kg once daily

Prophylactic dosage ranges

Standard dosing	Severe renal impairment
40 mg once daily	➡ 20 mg once daily
20 mg once daily	➡ 20 mg once daily

These adjustments do not apply to the haemodialysis indication.

Anti-Factor Xa monitoring is not normally required, but may be considered in those patients treated with LMWH who also have either an increased risk of bleeding (such as those with renal impairment, elderly and extremes of weight) or are actively bleeding.



COMMITTEE ON SAFETY
OF MEDICINES

The Yellow Card Scheme



Medicines and Healthcare products
Regulatory Agency

Safeguarding public health

Do you suspect that your patient has experienced an adverse drug reaction?

If so, don't delay, report it today.

Did you know there is a website dedicated to the Yellow Card Scheme?

www.yellowcard.gov.uk provides easy access to the electronic Yellow Card and enables health professionals to report *suspected* adverse drug reactions. The site also provides information about the Yellow Card Scheme and has links to other useful websites.

www.yellowcard.gov.uk

The Yellow Card Scheme acts as an early warning system for the identification of previously unrecognised reactions. It also enables us to investigate in detail established adverse drug reactions in order to identify risk factors, outcome of the adverse drug reaction and other factors that may affect clinical management. Better understanding of recognised reactions allows us to give advice on how medicines can be used more safely. The value of the Scheme has been demonstrated on many occasions through the early detection of drug safety issues.

An independent review of the scheme has recently been conducted to consider increasing access to the data and to strengthen the scheme. Further information is on the MHRA website.

The continued success of the Scheme is dependent on the vigilance of UK healthcare professionals and your willingness to report *suspected* adverse drug reactions. Every report can make a difference.

Contact information

For further information about the Yellow Card Scheme or to request Yellow Cards please contact us in one of the following ways:

✉ Write to us at: Medicines and Healthcare products Regulatory Agency, CSM FREEPOST, London, SW8 5BR

☎ Call the National Yellow Card Information Service on 0800 731 6789

🌐 Visit our website <http://www.mhra.gov.uk> email pharmacovigilance@mhra.gsi.gov.uk

You are helping the CSM and MHRA to protect public health.

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Dentists should notify a change of address by writing to Medical Mailing Company, Coltex House, Rectory Place, Loughborough, LE11 1TW, or by dialling the hotline number 0800 626387. Addresses supplied in connection with mailings on behalf of CSM and MHRA will not be used for other mailings without the permission of the individual concerned.