



COMMISSION ON
HUMAN MEDICINES

CURRENT PROBLEMS in Pharmacovigilance



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Internet version: <http://www.mhra.gov.uk/mhra/CurrentProblemsInPharmacovigilance>

Topical tacrolimus (Protopic ▼) and pimecrolimus (Elidel ▼): reports of malignancies

Topical tacrolimus 0.03% ointment (Protopic) and Topical pimecrolimus 1% cream (Elidel) are licensed for the treatment of atopic dermatitis (eczema) in adults and for children aged 2 years and over. The higher strength of Protopic (0.1%) is licensed for use in adults only.

European Safety Review

A Europe wide review of the risks and benefits of these products was completed in March 2006 following reports of skin cancers, lymphomas and other cancers occurring in association with the use of these two medicines. The conclusion was that it cannot currently be determined whether or not these malignancies were caused by these medicines. Therefore, the balance of benefits and risks remains favourable. The product particulars will be amended to inform prescribers and users of these reports, to minimise the potential risk to patients as follows.

In particular:

- Elidel 1% Cream should be used as a **second line treatment** for mild or moderate atopic dermatitis where treatment with topical corticosteroids is either inadvisable or not possible. Protopic will remain a second line treatment for moderate or severe atopic dermatitis in patients who are not adequately responsive to or are intolerant of topical corticosteroids.
- Treatment with Elidel Cream and Protopic Ointment should:
 - Only be initiated by physicians with experience in the diagnosis and treatment of atopic dermatitis.
 - Not be given to patients with congenital or acquired immunodeficiencies, or to patients on therapy causing immunosuppression.
 - Not be applied to malignant or to potentially malignant skin lesions.

In addition:

- Elidel Cream 1% and Protopic Ointment 0.03% are not recommended for use in children aged 2 years or below. Protopic Ointment 0.1% should not be used in children under 16 years of age .

- The frequency of administration of Protopic Ointment 0.03% in children should be limited to once daily.
- The lower strength of Protopic Ointment (0.03%), should be used in adults wherever possible.

Prescribers should use these products so as to minimise patient exposure and thereby reduce risk.

The following are recommended:

- The medicines should be applied thinly and to affected skin surfaces only.
- Treatment should be short term; continuous long-term use should be avoided.
- If no improvement occurs (after 6 weeks for Elidel, or 2 weeks for Protopic), or if the disease worsens, the diagnosis of atopic dermatitis should be re-evaluated and other therapeutic options considered.

Further information is available in the relevant NICE Guidelines: www.nice.org.uk.

Duloxetine (Yentreve ▼, Cymbalta ▼): need for monitoring

Duloxetine is a combined serotonin (5-HT) and noradrenaline (NA) reuptake inhibitor. It weakly inhibits dopamine reuptake with no significant affinity for histaminergic, dopaminergic, cholinergic and adrenergic receptors. It is licensed under the trade name Yentreve for the treatment of stress urinary incontinence in women. The recommended dose in this indication is 40 mg twice daily. It is also licensed for the treatment of major depressive disorder under the trade name Cymbalta. In this indication the recommended starting and maintenance dose is 60 mg once daily.

The most common adverse effects associated with its use are nausea, dry mouth, fatigue, insomnia and constipation. As with other drugs with similar pharmacological action (SSRIs and related antidepressants), isolated cases of suicidal thoughts and suicide attempts have been reported during duloxetine therapy or early after treatment discontinuation. Careful and frequent patient monitoring during treatment is recommended, particularly for high risk groups.

Patients (and caregivers) should be alerted about the need to monitor for the emergence of suicidal thoughts/behaviour and to seek medical advice immediately if these symptoms present. Prescribers are also reminded that due to the risk of withdrawal reactions treatment with duloxetine should not be stopped suddenly. Withdrawal should be via gradual dose tapering over a period of at least two weeks.

The MHRA upheld a complaint about a dosing guide provided by Eli Lilly and Boehringer Ingelheim to healthcare professionals regarding Cymbalta and its use

“For depressed patients *with general aches and pains*”. Eli Lilly and Boehringer Ingelheim agreed to suspend use of this dosing guide and amend the claim.

Tenofovir (Viread ▼): interactions and renal adverse effects

Tenofovir is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected adults over 18 years of age. Earlier this year the European Agency for the Evaluation of Medicinal Products issued a statement regarding efficacy and safety concerns associated with the co-administration of tenofovir and didanosine. The interaction between tenofovir and didanosine results in increased didanosine levels with a subsequent risk of didanosine related adverse effects, such as pancreatitis and lactic acidosis.

In order to avoid over-exposure to didanosine, a dose reduction of didanosine has been advised when used in combination with viread, but this has now been associated with reports of a high rate of virological failure. Therefore this combination of drugs is **not** recommended. Should this combination be considered necessary in an individual patient they should be carefully monitored for efficacy and adverse effects.

Renal adverse effects, including diabetes insipidus, associated with tenofovir continue to be reported. Monitoring of renal function (creatinine clearance and serum phosphate) is recommended before and during tenofovir treatment.

Linezolid (Zyvox ▼): severe optic neuropathy

*Visual function should be routinely monitored in those patients on prolonged (**greater than 28 days**) linezolid therapy and evaluated in all patients with new visual symptoms*

Linezolid is a synthetic antibacterial agent that belongs to a new class of antimicrobials, the oxazolidinones. It is indicated for the treatment of nosocomial- and community-acquired pneumonia and for complicated skin and soft tissue infections that are known, or suspected, to be caused by methicillin- or vancomycin-resistant Gram positive bacteria. Treatment with linezolid should only be initiated in a hospital environment, after consultation with a relevant specialist. The safety and efficacy of linezolid therapy has not been established beyond 28 days in controlled clinical trials. Based on postmarketing experience, severe optic neuropathy that has progressed to blindness has been reported rarely in patients treated with linezolid¹⁻³. These cases have occurred primarily in patients who have received linezolid for longer than the maximum

recommended duration of 28 days. In some cases, vision has been reported to recover after early withdrawal of the drug, but this process may take some months. Information for prescribers and patients has been updated to reflect the severity of this adverse drug reaction.

If optic neuropathy occurs, the continued use of linezolid in these patients should be balanced against the potential benefits.

Physicians are advised to:

- Warn patients to immediately report any symptoms of visual impairment, including changes in visual acuity, changes in colour vision, blurred vision or visual field defect.
- Ensure that any patient experiencing new visual symptoms, regardless of treatment duration, is promptly evaluated and, if necessary, referred to an ophthalmologist.
- Regularly monitor the visual function of all patients who may require treatment for longer than the recommended 28 days.

1. Saijo T et al. *Am J Ophthalmol.* 2005; 139(6): 1114-6
2. McKinley SH and Foroozan R *J Neuroophthalmol.* 2005; 25(1): 18-21
3. Lee E et al. *Clin Infect Dis* 2003; 37(10): 1389-91

CosmoFer ▼ and high risk of anaphylactoid reactions

CosmoFer, an iron dextran complex, and Venofer, iron sucrose, are used for the parenteral treatment of iron deficiency in patients who are intolerant to oral iron preparations.

Acute, severe anaphylactoid reactions have been associated with parenteral iron preparations, in some cases with fatal outcomes. In order to reduce the risk of potentially life threatening anaphylactoid reactions, prescribers are reminded to test dose patients and have anaphylactic emergency measures close at hand. Full prescribing directions are available within the product information for CosmoFer and Venofer.

Drotrecogin alfa (activated) (Xigris ▼): risk-benefit in the management of sepsis

Adhere to prescribing recommendations

Drotrecogin alfa (activated) (Xigris[®]) is a recombinant human activated Protein C. It is indicated for the treatment of adults with severe sepsis with multiple organ failure when added to best standard care. Marketing authorisation

was granted on the basis of the results of one study known as the PROWESS study.

A randomised, placebo-controlled clinical trial called the ADDRESS study, which recruited patients with less severe sepsis than the PROWESS study was stopped prematurely because an interim analysis based on approximately 1300 patients treated with drotrecogin alfa (activated), indicated a low likelihood of the trial being capable of detecting a statistically significant reduction in 28-day mortality in patients at lower risk of death from sepsis.

An increased mortality with drotrecogin alfa (activated) was detected in patients with single organ dysfunction (17.4% vs 14.8% - relative risk 1.17; 95% CI 0.95-1.46) but not in those with multiple organ dysfunction (20.7% vs 21.9% - relative risk 0.94; 95% CI 0.73-1.22). The analysis of the ADDRESS study showed a statistically significant increase in the risk of death in patients treated with drotrecogin alfa (activated) who had recent surgery and a single organ system failure.

Recent surgery (within 30 days prior to study entry) was also associated with a higher risk of serious bleeding during infusion of drotrecogin alfa (activated) (3.63% vs 1.59% in patients without recent surgery). The outcome in the ADDRESS study was reproduced (albeit not statistically significant) in a post-hoc analysis of the data from the PROWESS study.

The analysis also suggested that the treatment outcome may be better if patients are treated with drotrecogin alfa (activated) as soon as possible after the onset of severe sepsis with multiple organ dysfunction, preferably within 24 hours. Overall the data indicate that the greatest care is required when considering patients for treatment with drotrecogin alfa (activated).

Prescribers are reminded:

- A positive mortality benefit has only been demonstrated for drotrecogin alfa (activated) in adults with **severe sepsis associated with multiple organ dysfunction when added to best standard care**. Children and patients with single organ dysfunction have not been shown to benefit.
- Drotrecogin alfa (activated) should only be administered by specialists in the management of sepsis in an appropriately equipped and staffed setting.
- Treatment should be started within 48 hours but **preferably within 24 hours**, of the onset of severe sepsis.
- Patients with single organ failure, especially those who have been subjected to surgery in the previous month may be at a particularly high risk of death and should not receive drotrecogin alfa (activated).

Rosuvastatin (Crestor ▼): introduction of 5 mg starting dose

Rosuvastatin calcium (Crestor) is a potent selective 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin). Previously we reminded prescribers that as with other statins, muscle toxicity is a recognised, dose-related adverse reaction, leading in rare cases to rhabdomyolysis¹.

New 5 mg starting dose

The 5 mg dose has been licensed in Europe to be used as the recommended starting dose in **Asians** (who experience higher plasma levels of rosuvastatin than Caucasians) and patients with pre-disposing factors for myopathy, which include:

- Moderate renal impairment (creatinine clearance < 60 ml/min).
- Hypothyroidism.
- Personal or family history of hereditary muscular disorders.
- Previous history of muscle toxicity with another HMG-CoA reductase inhibitor or fibrate.
- Alcohol abuse.
- Patients > 70 years of age.
- Concomitant use of fibrates.

Other patients may be started on either 5 mg or 10 mg depending on cholesterol level and future cardiovascular risk as well as the potential risk for adverse reactions.

All patients should be started on 5 mg or 10 mg of rosuvastatin and should only be titrated to a higher dose after a 4 week trial. The 40 mg dose should only be prescribed under specialist supervision as it is contraindicated in patients with predisposing risk factors for muscle toxicity.

Prescribers are reminded that patients who are switched over from another HMG-CoA reductase inhibitor should also start with the 5 mg or 10 mg dose of rosuvastatin depending on their cholesterol level and future cardiovascular risk as well as the potential risk for adverse events.

Patients receiving any statin should be asked to report muscle pain, weakness or cramps to their prescriber as soon as possible, and to 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.

1. MHRA/CSM Current Problems in Pharmacovigilance 2004; 30: 1-2.

Osteonecrosis of the jaw with bisphosphonates

Osteonecrosis of the jaw has been reported in patients treated with bisphosphonates

Bisphosphonates are indicated for:

- The prevention and/or treatment of osteoporosis [alendronic acid (Fosamax and Fosamax Once Weekly, Fosavance), ibandronic acid (Bondronat), risedronate sodium (Actonel and Actonel Once weekly), disodium etidronate (Didronel PMO)].
- The treatment of Paget's disease [disodium etidronate (Didronel), disodium pamidronate (Aredia), tiludronic acid (Skelid)].
- Hypercalcaemia of malignancy [(disodium pamidronate, ibandronic acid (Bondronat) sodium clodronate (Bonefos and Loren), zoledronic acid (Zometa)].
- The prevention of skeletal fracture events [ibandronic acid (Bondronat) and zoledronic acid (Zometa)].

Osteonecrosis of the jaw has been reported in association with bisphosphonates. The majority of reports have been in cancer patients treated with intravenous bisphosphonates; in the UK we have received 62 spontaneous reports of osteonecrosis in patients receiving zoledronic acid, 9 reports in patients receiving pamidronate and 4 reports in patients receiving ibandronic acid and 2 reports with sodium clodronate. There have also been reports with oral bisphosphonates.

We have also received 8 spontaneous reports of osteonecrosis in association with the oral bisphosphonate alendronic acid and one report with risedronate sodium. World-wide many of the patients who developed osteonecrosis while on bisphosphonates were also receiving chemotherapy and/or corticosteroids.

The majority of reported cases have been associated with dental procedures such as tooth extraction, and many had signs of local infection including osteomyelitis.

- A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, corticosteroids and poor oral hygiene).
- While on treatment, patients with concomitant risk factors should avoid invasive dental procedures if possible.

For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition.

For patients requiring dental procedures, there are no data available to suggest whether discontinuation

of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. The clinical judgment of the treating physician should guide the management plan of each patient based on an individual benefit-risk assessment.

High dose inhaled steroids: new advice on supply of steroid treatment cards

Patients who require prolonged high dose inhaled steroids are at risk of systemic side effects and should be issued with a steroid treatment card

Inhaled steroids are important and effective preventative treatments for asthma and have a well-established safety track record, when used at recommended doses. Prolonged use of high doses of inhaled steroid carries a risk of systemic side effects, including adrenal suppression or crisis, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma¹. We have previously highlighted the risks associated with exceeding the recommended doses of inhaled steroids, especially in children² (see maximum doses in associated table).

Prescribers are reminded that fluticasone (Flixotide) should normally be used at half the dose of beclomethasone (CFC containing) or budesonide because of its greater potency.

Steroid treatment cards can serve to educate patients about their treatment and alert clinicians to the possibility of adrenal suppression and need for steroid therapy. **It is advised that steroid treatment cards should be routinely provided for patients (or their parents/carers) who require prolonged treatment with high doses of inhaled steroids.**

High dose may be considered as:

- 'Off-label' high doses of inhaled steroids.
- Maximal licensed doses of inhaled steroids when used in conjunction with other steroids (such as oral steroids).
- Use of inhaled steroids with concomitant medicines that inhibit their metabolism (cytochrome P450 inhibiting drugs: e.g. HIV protease inhibitors).

Other high-risk patients should be provided with a steroid card, at the discretion of the prescriber/pharmacist

Prescribers are reminded that it is important to review therapy regularly and titrate down to the lowest dose at which effective control of asthma is maintained. Patients who are not controlled on the maximum licensed dose of inhaled steroids, despite the addition of other therapies, should be referred to a specialist.

Maximum licensed doses of inhaled corticosteroids for children and adolescents

Beclomethasone	400mcg/day (age not stated)
Budesonide	800mcg/day (12 years of age <i>and under</i>)
Fluticasone	400mcg/day (4 -16 years)
Mometasone	800mcg/day (12 years <i>and older</i>)

1. MCA/CSM Current Problems in Pharmacovigilance. 1998; 24: 5.
2. MCA/CSM Current Problems in Pharmacovigilance. 2002; 28: 7.

Local reactions associated with pre-school d/DTaP-IPV boosters

Extensive limb swelling following d/DTaP IPV boosters is common but transient

Acellular pertussis replaced whole cell pertussis in DTP¹ vaccines² (DTaP and DTwP respectively) in the UK immunisation programme in September 2004³. Vaccines containing acellular pertussis⁴ are generally less reactogenic than those containing whole cell pertussis⁵, particularly in older children.

However, booster doses of vaccines containing acellular pertussis are associated with an increased risk of injection site reactions^{6,7}, compared to primary vaccination. Some of these affect the entire limb, and may involve blistering around the site of swelling. Such reactions usually develop within 24 hours of vaccination and recover without sequelae within ~5 days.

The risk appears to be dependent on the number of prior doses of DTaP vaccine, with a greater risk following the 4th and 5th doses, although such reactions to a DTaP booster may also occur in children who have been primed with one or more doses of a DTwP vaccine. Such reactions do not contraindicate further doses of DT or DTaP vaccine.

If a child presents with signs of extensive limb swelling following d/DTaP-IPV pre-school vaccination it is important to carefully consider whether this may be a recognised injection site reaction. In the absence of clinical or laboratory signs of infection, antibiotics may be ineffective and unnecessary. More detailed information is available on the MHRA website: www.mhra.gov.uk

- 1 Diphtheria, tetanus and pertussis.
- 2 This was accompanied by a switch from use of live oral polio (OPV) vaccine to inactivated polio vaccine (IPV).
- 3 www.dh.gov.uk/assetRoot/04/08/73/47/04087347.pdf.
- 4 Including DTaP in combination with other antigens.
- 5 Jefferson *et al.* Vaccine 2003; 21: 2003-14.
- 6 Gold *et al.* Medical journal of Australia 2003; 179:191-194.
- 7 Rennels *et al.* Pediatrics 2000; 105(1).

Salmeterol (Serevent) and formoterol (Oxis, Foradil) in asthma management

Patients taking long-acting beta₂ agonists should also be taking inhaled steroids, and should be monitored closely for therapeutic response in the early months of treatment

Prescribers were previously reminded¹ to follow the British Thoracic Society (BTS) guidelines for the treatment of asthma². The final results from the Salmeterol Multi-Centre Asthma Research Trial (SMART), conducted in the United States, showed that patients who did not use inhaled corticosteroids with salmeterol had a higher incidence of asthma-related adverse events than patients who did use inhaled corticosteroids with salmeterol, particularly African-American patients.

The main findings of the SMART study for the primary endpoint of combined respiratory-related death or life threatening experience are summarised in the table below. It is not possible to rule out similar concerns for formoterol.

Prescribers are reminded that:

- patients given salmeterol or formoterol should always be prescribed an inhaled corticosteroid.
- patients with acutely deteriorating asthma should not be initiated on salmeterol or formoterol.
- patients should be monitored closely during early treatment.

It is not clear if underlying genetic variations are responsible for the differences observed between African-American and Caucasian patients in this study, and whether these results are relevant to the UK population.

- 1 MCA/CSM Current Problems in Pharmacovigilance. 2003; 29: 5.
- 2 BTS/SIGN. Management of Asthma. Thorax. 2003;54:1-94.

Main findings from the SMART study

Patient group	Number of primary endpoint events /number of patients		Relative Risk (95% confidence intervals)
	salmeterol	placebo	
All patients	50/13,176	36/13,179	1.40 (0.91, 2.14)
Patients using inhaled steroids	23/6,127	19/6,138	1.21 (0.66, 2.23)
Patients not using inhaled steroids	27/7,049	17/7,041	1.60 (0.87, 2.93)
African-American patients	20/2,366	5/2,319	4.10 (1.54, 10.90)

Risk in bold is statistically significant at the 95% level.

Risk of QT interval prolongation with methadone

Methadone is indicated for treatment of opioid drug addiction, and is used as an analgesic for moderate to severe pain or as an anti-tussive. Spontaneous reports in Europe and a literature article¹ have highlighted the risk of QT interval prolongation in patients taking methadone, especially those on high doses.

It is recommended that patients with the following risk factors for QT interval prolongation are carefully monitored whilst taking methadone: heart or liver disease, electrolyte abnormalities, concomitant treatment with CYP 3A4 inhibitors, or medicines with the potential to cause QT interval prolongation. In addition any patient requiring more than 100mg of methadone per day should be closely monitored. Further advice is included in the product information.

1. Krantz MJ, et al. Ann. Intern. Med. 2002; 137: 501-504.

Tamsulosin (Flomax) and Intraoperative Floppy Iris Syndrome (IFIS)

Tamsulosin (Flomax) is an alpha-blocker licensed for benign prostatic hyperplasia (BPH). Recently tamsulosin has been identified as a cause of the Intraoperative Floppy Iris Syndrome (IFIS), a newly diagnosed variant of small pupil syndrome that may lead to increased procedural complications during cataract surgery¹.

The condition is characterised by the combination of a flaccid iris that billows in response to intraoperative irrigation currents, progressive intraoperative miosis despite pre-operative dilation with standard mydriatic drugs, and potential prolapse of the iris toward the phaco-emulsification or side incisions.

The majority of cases have been observed in patients on, or previously treated with, tamsulosin, but cases have also

been reported with other alpha-blockers including alfuzosin (Xatral) and doxazosin (Cardura).

Prescribers are advised that the initiation of treatment in patients awaiting cataract surgery is not recommended. Stopping alpha-blocker therapy 1-2 weeks prior to cataract surgery has been suggested to be helpful but this has yet to be established.

During pre-operative assessment, cataract surgeons and ophthalmic teams are advised to consider whether patients scheduled for cataract surgery are being or have been treated with alpha-blockers in order to ensure that appropriate measures are in place to manage IFIS during surgery.

1. Chang, D.F. & Campbell, J.R. J Cataract Refract Surg 2005; 31: 664-673.

Cardiovascular safety of NSAIDs and selective COX-2 inhibitors

No changes to prescribing advice on NSAIDs

Restrictions for all COX-2 inhibitors, including lumiracoxib, have been extended to include peripheral artery disease

Recent evidence of an increased risk of myocardial infarction and cerebrovascular events have resulted in a Europe-wide review of the cardiovascular safety data of COX-2 inhibitors (coxibs) and non-steroidal anti-inflammatory drugs (NSAIDs).

Conclusions so far:

The available evidence suggests that selective COX-2 inhibitors, as a class, cause a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) compared with placebo, and the risk may increase with dose and duration of exposure.

No firm conclusions can be drawn regarding the cardiovascular safety of naproxen, ibuprofen and diclofenac relative to one another, or selective COX-2 inhibitors. There is some evidence that naproxen may have a lower thrombotic risk than selective COX-2 inhibitors.

Any cardiovascular risk of non-selective NSAIDs is likely to be small and associated with continuous long-term treatment and higher doses. In addition, all NSAIDs and selective COX-2 inhibitors may cause renal adverse effects potentially leading to oedema, hypertension and heart failure.

Over the Counter (OTC) ibuprofen

The safety profile of Ibuprofen at OTC doses is reassuring, particularly in respect of gastrointestinal adverse effects. The cardiovascular risk associated with prolonged treatment and high doses of ibuprofen is not clear, however short-term use at lower OTC doses is unlikely to be associated with any increased risk.

Key points on the use of non-selective NSAIDs and selective COX-2 inhibitors are summarised below:

Non-selective NSAIDs

- Prescribing should be based on overall safety profiles of NSAIDs (particularly gastrointestinal safety) as set out in product information, and risk factors for individual patients.
- Switching treatment between non-selective NSAIDs is not justified on the available evidence on thrombotic risk.
- Ibuprofen is the non-selective NSAID associated with the lowest level of gastro-intestinal risk and for this reason has been available for many years for short-term use without a prescription. Increased thrombotic risk is very unlikely for short-term low dose treatment.

Selective COX-2 inhibitors

- European-wide contraindications for patients with established ischaemic heart disease (IHD), cerebrovascular disease has now been extended to include patients with peripheral artery disease.
- For patients with risk factors for cardiovascular events, individual risk assessment is appropriate.
- Cardiovascular contraindications and warnings apply to all licensed COX-2 inhibitors, including lumiracoxib, which has recently been launched. Please report all suspected adverse drug reactions relating to lumiracoxib.

All NSAIDs and selective COX-2 inhibitors

- All patients should take lowest effective dose of NSAIDs or COX-2 inhibitors for the shortest time necessary to control symptoms.
- Co-prescription with aspirin should be avoided unless absolutely necessary.

A more detailed summary of the evidence discussed above is available on the MHRA website www.mhra.gov.uk

Erythromycin and other macrolides: focus on interactions

Erythromycin is a very widely used antibiotic and is a substrate and inhibitor of cytochrome P450 (CYP3A) enzymes. Recent literature^{1, 2} has highlighted the potential for interactions between macrolides such as erythromycin and other medicines resulting in cardiotoxic effects.

Important interactions involving erythromycin/ other macrolides are listed in Appendix 1 of the British National Formulary. The following are not comprehensive lists.

- **The following should not be co-administered with erythromycin:** amisulpride, simvastatin, ergotamine, dihydroergotamine, tolterodine, cisapride, pimozide, terfenadine and mizolastine.
- **Erythromycin may increase serum concentrations of CYP metabolised drugs including:** atorvastatin, bromocriptine, carbamazepine, cilostazole, cyclosporin, clozapine, midazolam, phenytoin, quinidine, tacrolimus, rifabutin, theophylline*, valproate, alfentanil, zopiclone, warfarin and digoxin.
- **Increased erythromycin levels may occur with other CYP3A inhibitors,** such as 'azole' anti-fungals, some calcium channel blockers (diltiazem, verapamil), anti-HIV protease inhibitors (e.g. amprenavir, ritonavir, saquinavir).

**Theophylline also decreases erythromycin levels.*

Prescribers are reminded that cytochrome P450 inhibition caused by macrolides may have a slow onset and persist for several days after cessation of treatment.

Pharmacodynamic interactions:

Erythromycin can increase the ECG QT interval and may rarely be associated with arrhythmias, such as *torsades de pointes*. This risk is increased when erythromycin is co-administered with other drugs that increase QT interval and with type 1(a) and type III anti-dysrhythmics (e.g. disopyramide, quinidine, amiodarone).

Co-administration of drugs which increase QT interval and have pharmacokinetic interactions with erythromycin (e.g. mizolastine, cisapride, terfenadine) may be particularly hazardous and should be avoided.

1. Grant R. Wilkinson. N. Engl J Med 2005; 352: 2211-21.
2. Wayne A. Ray et al. N. Engl J Med 2004; 351: 1089-96.

Glucosamine adverse reactions and interactions

Glucosamine is a nutritional supplement taken by many people for joint pain and other symptoms of osteoarthritis. It is not licensed as a medicinal product and the efficacy of glucosamine for the treatment of the symptoms of osteoarthritis has yet to be established¹

Patients with seafood allergies should avoid taking glucosamine as it is manufactured by processing the crushed shells of crustaceans and therefore may lead to an allergic reaction in individuals who are allergic to seafood.

We have received 7 reports suggesting an interaction between warfarin and glucosamine. In these cases patients who had previously stable INRs on warfarin had an increase in their INR after they started taking glucosamine supplements. The mechanism of any interaction is unclear however, **patients on warfarin are recommended not to take glucosamine.**

1. Towheed TE, Maxwell L, Anastassiades TP, et al. Cochrane Database Systematic Reviews. Issue 2.

Isotretinoin (Roaccutane): psychiatric adverse reactions

Isotretinoin (13-cis-retinoic acid) is indicated for the treatment of severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy.

Warnings about the possible occurrence of depression and other psychiatric symptoms were first added to the Summary of Product Characteristics (SPC) for isotretinoin in 1998.

Since 1998 these warnings have been expanded and now include warnings about depression, worsening depression in those with a history of depression, anxiety, aggressive tendencies, mood alterations, psychotic symptoms, abnormal behaviour, suicidal thoughts and behaviour including attempts and accomplished suicide occurring in patients treated with isotretinoin.

In June 2005, an Expert Working Group of the Committee on Safety of Medicines met to consider all available data relating to psychiatric reactions with isotretinoin, including non-clinical data, clinical trials, published literature, spontaneous reports and epidemiological studies.

The pre-clinical data did not indicate any evidence of psychiatric or CNS effects. Data from clinical trials conducted before licensing did not suggest that isotretinoin was associated with depression, however, these studies were not designed to identify psychiatric adverse reactions and were too small to identify rare reactions.

Recent studies specifically designed to evaluate psychiatric effects have reported conflicting results, with some indicating an association with treatment and others not.

The available epidemiological evidence has not identified an association between isotretinoin and depression and suicide, however there were many limitations associated with the studies which may account for this finding.

A review of spontaneously reported cases of psychiatric reactions did not identify any specific risk factors for psychiatric adverse reactions and the use of isotretinoin. The review included 9683 reports of psychiatric disorders suspected to be associated with the use of isotretinoin, including 112 cases of depression, suicide attempt or suicidal ideation which described a positive rechallenge.

The Expert Working Group concluded that the product information reflected the currently available evidence. It is recommended that patients starting isotretinoin should be advised about possible mood changes and monitored for signs of depression and referred for appropriate treatment if necessary.

Cardiac arrhythmias associated with antipsychotic drugs

An expert working group of the CSM, established to consider the risks of cardiac arrhythmias occurring during treatment with antipsychotic drugs made the following recommendations:

ECG and electrolyte monitoring

- The need for an ECG should be judged on the risks to the patient from relevant previous medical history, family history and clinical examination. The need for ECG monitoring while on therapy will also be influenced by any ECG result at baseline.
- Whenever an ECG is conducted a record of the prevailing heart rate should be made.

Baseline ECG

- The elderly, those with a personal or family history of heart disease or any cardiac abnormalities on examination would benefit most from a base line ECG.
- An ECG should be performed as soon as possible especially to diagnose: ischaemic heart disease, structural heart disease, QT prolongation.

During therapy

- Patients should always be given the lowest dose of antipsychotic medication that controls symptoms.
- Polypharmacy should be avoided. Particular attention should be paid to avoiding co-prescription of drugs that interact either through kinetic or dynamic interactions.
- Any patient taking antipsychotic drugs who experiences palpitations or any other symptoms suggestive of cardiac disease should have an ECG.
- If the QT interval is prolonged then dose reduction should be considered.
- If the QT interval exceeds 500msec the drug should be discontinued unless there are compelling reasons to continue it.
- The need for ECG at dose escalation should be considered.
- Potassium levels should be monitored before and during therapy and particularly during periods of acute intercurrent illness such as gastrointestinal upset.

A Europe-wide review of the product information for antipsychotics drugs, based on the work of the CSM Expert Working Group, has recently been completed. Further information including the report of the European review can be found on the MHRA website www.mhra.gov.uk.

HRT and tibolone (Livial): update on the risk of endometrial cancer

The proliferative effect of oestrogen-only HRT on the endometrium is well recognised¹ and adding a progestogen for at least 12 days of the month opposes this effect and protects the endometrium.

Tibolone (Livial) is licensed for the same indications as conventional HRT. Tibolone and its metabolites possess progestogenic, oestrogenic and androgenic properties. Tibolone has previously been widely regarded as being 'endometrial safe'.

Estimated standardised incidence rates for endometrial cancer and breast cancer

	Type of HRT used at recruitment				
	Never use (n, 95%CI)	Oestrogen- only (n, 95%CI)	Tibolone (n, 95%CI)	Cyclic combined (n, 95%CI)	Continuous combined (n, 95%CI)
Endometrial cancer	3 (3-3)	5 ^a (4-8)	6 (5-8)	3 (3-4)	2 (2-3)
Breast cancer*	14 (13-14)	18 (17-20)	20 (18-23)	28 (26-30)	29 (28-31)

Figures based on use per 1000 never-users of HRT or current users of tibolone or HRT over a 5 year period.

*These values differ from those previously presented. The figures in the SPC are based on generalised incidence rates that are intermediate between UK and USA incidence rates in the mid-1980's and are expressed over a 15 year period; those in the table are based on the values observed for never-users of HRT in the MWS and are expressed over a 5 year period.

^a Results from a meta-analysis of worldwide data¹ suggest a figure of between 6 and 8 per 1000.

New data on endometrial safety

A large UK observational study, the Million Women Study (MWS), recently reported its latest findings on endometrial cancer². A summary of the results is provided in the table above.

A study using the General Practice Research Database (GPRD)³ also recently reported a similar increase in the risk of endometrial cancer in tibolone users compared with users of combined sequential HRT (RR = 1.5, 1.0 – 2.3).

Effect of body mass index (BMI)

The risk of endometrial cancer in every 1000 women not taking HRT over a 5 year period increases with increasing BMI (2 cases in women with a BMI <25 kg/m² to 6 cases in women with a BMI greater than or equal to 30 kg/m²).

The MWS found that the effect of tibolone on the endometrium was most apparent in women with lower BMIs, while the beneficial effect of combined HRT was most apparent in women with a higher BMI.

Balancing the risks

Prescribers were previously informed about the risk of breast cancer in HRT and tibolone users⁴.

The latest data from the MWS also provides updated incidence rates for breast cancer which can be directly compared with those for endometrial cancer in the same population (see table above).

Both these risks should be taken into consideration when deciding which type of treatment is most suitable for women with an intact uterus.

Advice for prescribers

- The benefits of short-term HRT and/or tibolone for treating menopausal symptoms are considered to outweigh the risks in the majority of women.
- 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.
- For women without a uterus, oestrogen-only therapy is appropriate.
- In women with an intact uterus, the risks of endometrial cancer and breast cancer for each woman should be carefully assessed, taking into account her individual risk factors and bearing in mind the frequency and characteristics of both cancers, in terms of their response to treatment, morbidity and mortality.
- Tibolone (and continuous combined HRT preparations) should only be used in women who have not had a natural menstrual bleed for at least 1 year.
- Tibolone, like all HRT, is contraindicated in women with undiagnosed vaginal bleeding except breakthrough bleeding occurring during the first 6 months of treatment. All unexplained bleeding should be investigated, including bleeding after treatment has stopped, to exclude endometrial malignancy.
- The increased risk of endometrial cancer associated with increased BMI is greater than the increased risk due to HRT and/or tibolone.

1. Grady D et al., *Obstet & Gynaecol.* 1995; 85: 304-313.
2. Million Women Study Collaborators, *Lancet* 2005; 365: 1543-5.
3. De Vries et al., *Drug Safety* 2005; 28(3): 241-249.
4. MHRA/CSM Current Problems in Pharmacovigilance. 2003; 29: 1-3.



Reminders

Hypoglycaemia unawareness on transferring insulins

Transferring a patient to a new type or brand of insulin should be done under strict healthcare professional supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente) and species (i.e. animal to human) may result in the need for a change in dose.

Some patients who have experienced hypoglycaemic reactions after transfer from animal to human insulin have reported that the early warning symptoms of hypoglycaemia were less pronounced or different from those experienced with their previous insulin. Although clinical evidence of a difference between human and animal insulin with regard to unawareness of hypoglycaemia is inconclusive, if an individual considers that human insulin is responsible for the loss of “warning” it may be advisable to revert to animal insulin.

Withdrawal of co-proxamol (Distalgic, Cosalgic, Dolgesic)

Co-proxamol (a combination of paracetamol and dextropropoxyphene) was indicated for the management of mild to moderate pain. It was involved in 300-400 deaths each year, of which around a fifth were accidental. Many deaths involved people taking co-proxamol that had not been prescribed for them.

UK research¹ showed that co-proxamol alone was implicated in almost one-fifth of drug related suicides, second only to tricyclic antidepressants. Since 1985 advice aimed at the reduction of co-proxamol toxicity and fatal overdose has been provided, unfortunately this has not been effective.

In April 2004, a risk:benefit review of co-proxamol products was undertaken. This included a public call for information on the risks and benefits of co-proxamol and the establishment of a CSM Working Group on Pain Management.

Withdrawal of co-proxamol

The conclusion of the risk:benefit review was that co-proxamol should be withdrawn from the market on the grounds that the risks outweighed the benefits. It was decided to withdraw co-proxamol over an extended period of time in order to allow long term users an opportunity to move to suitable alternatives.

Co-proxamol was removed from prescribing formularies in some parts of the UK (e.g. Northern Ireland) several years ago. The general withdrawal of co-proxamol will be phased over a period of up to 36 months. Some manufacturers have already withdrawn co-proxamol and a few will phase the withdrawal until the end of 2007.

To ensure patients are transferred in a managed way we suggest that patients are moved as soon as possible from co-proxamol to suitable alternatives. Data suggests that the number of prescriptions for co-proxamol is steadily dropping. However we recognise that there is a small group of patients who are likely to find it very difficult to change or where there is an identified clinical need; when alternatives appear not to be effective or suitable. For these patients, continued provision of co-proxamol through normal prescribing may continue until the cancellation of the licences at the end of 2007. After this time a provision will remain for the supply of unlicensed co-proxamol, on the responsibility of the prescriber.

1. Hawton K, et al. British Medical Journal 2003; 326: 1006-1008.
2. Advice from the CSM Expert Group on Analgesic options in mild to moderate pain (mhra.gov.uk).

Intravenous human normal immunoglobulin (IVIg) and thromboembolic adverse reactions

Caution should be exercised when administering intravenous immunoglobulin to patients with pre-existing risk factors for thrombotic events

It is recognised that intravenous human normal immunoglobulin (IVIg) may very rarely induce thromboembolic events such as myocardial infarction, stroke, pulmonary embolism and deep vein thrombosis. It is assumed that this is due to a relative increase in blood viscosity through the influx of immunoglobulin in at-risk patients. Prescribers are reminded to exercise caution when prescribing and infusing intravenous immunoglobulin in obese patients and those with pre-existing risk factors for arterial or venous thrombotic events.

NSAIDs and infertility

Prostaglandins are involved in processes relating to fertility such as ovulation and implantation. Consequently, NSAIDs may impair female fertility and are not recommended in women attempting to conceive.

In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of NSAIDs should be considered.

Patients across the UK may report suspected adverse reactions

For over 40 years, the Yellow Card Scheme has been the cornerstone of medicines safety monitoring in the UK. Yellow Card reports on suspected adverse drug reactions are used to identify signals of potential safety issues.

The ongoing success of the Yellow Card scheme depends on the continued support of health professionals. It is vitally important that we continue to receive reports from health professionals, who submit approximately 18,000 reports of suspected adverse reactions each year.

We believe patient Yellow Card reporting will complement, not replace the Yellow Card reports we receive from health professionals.

Patients (and their carers) can report suspected adverse reactions on any medicine (including over-the-counter and herbal remedies) through the Yellow Card Scheme using any of the following methods:

- Paper - Patient Yellow Cards will be available in GP surgeries, community pharmacies and other outlets.
- Electronic - Patient Yellow Cards can be completed online at www.yellowcard.gov.uk.
- Telephone - Patient Yellow Cards can be submitted by calling freephone 0808 100 3352.

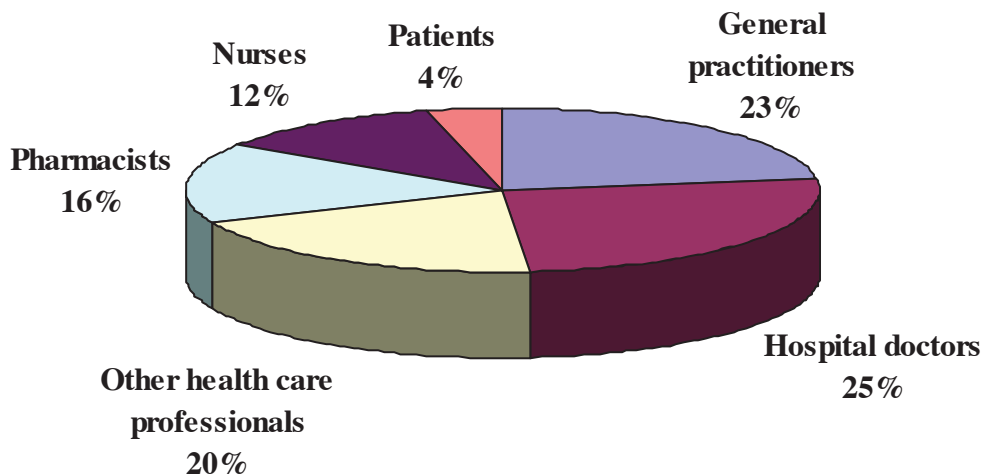
What to expect after a report has been submitted

The individual reporting the adverse reaction will receive an acknowledgement along with a copy of the adverse reaction report. At the request of the reporter a copy can also be sent to the patient's GP and or consultant. In some circumstances a request for further information may be made with either the reporter or the patient's doctor directly (provided the patient has given permission).

Confidentiality

The information provided within patient reports is treated in the same manner as health professional reports and are kept safe, secure and confidential under the terms of the Data Protection Act. Personal information will not be passed to any person outside the MHRA without the reporters express permission.

In 2005 the MHRA received 20,925 reports of suspected adverse reactions. The pie chart below provides a summary of who reported those adverse reactions.



We are grateful to all our reporters for this vital contribution to monitoring the safety of medicines in clinical use.

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