

# Drug Safety Update



## Latest advice for medicines users

The monthly newsletter from the **Medicines and Healthcare products Regulatory Agency** and its independent advisor the **Commission on Human Medicines**

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Welcome to the first issue of *Drug Safety Update* for 2008. We start the year with an update on a widely used class of medicines – statins. Turn to page 2 for information about the potential interactions that may occur with these medicines. Also in this issue: some important information about potential CNS toxicity with methylthionium chloride (methylene blue) in patients who are also receiving serotonergic drugs (page 5).

The Yellow Card scheme update this month discusses how Yellow Card data are available for researchers who are planning to conduct studies (page 8).

Healthcare professionals who treat people with asthma may find useful a Hot Topic article this month, which summarises current knowledge and advice about the role of long-acting  $\beta_2$  agonists in the management of this condition (page 9).

Please continue to email your comments about *Drug Safety Update* to the address below. Alternatively, complete our reader survey online at [www.mhra.gov.uk/mhra/drugsafetyupdate](http://www.mhra.gov.uk/mhra/drugsafetyupdate).

From all at the *Drug Safety Update* team, we wish you a healthy and successful 2008, and we hope that the bulletin is a useful resource for you throughout the year.

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**The Medicines and Healthcare products Regulatory Agency** is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe.

**The Commission on Human Medicines** gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

# Drug safety advice

## Statins: interactions, and updated advice for atorvastatin

**Keywords:** statins, atorvastatin, drug interactions, cytochrome P450, CYP3A4, ciclosporin, macrolides, clarithromycin, itraconazole, protease inhibitors, calcium-channel blockers, grapefruit juice, warfarin

**Drug interactions may increase the risk of adverse effects, or reduce the effectiveness of statin treatment. Updated prescribing advice for atorvastatin provides detailed recommendations for dose restrictions when used with some other drugs**

Statins are effective and widely used treatments for the prevention of cardiovascular events. Consideration of possible drug interactions is important because comorbidity is common in statin users. Interactions may increase the risk of serious adverse reactions (such as myopathy or rhabdomyolysis) or, in some cases, reduce the effectiveness of treatment.

This article summarises the most important and common interactions with statins. It includes updated advice for atorvastatin (Lipitor), particularly potential interactions with clarithromycin, itraconazole, and ciclosporin. Healthcare professionals should refer to Summaries of Product Characteristics for full details of interactions.

### Simvastatin and atorvastatin: interactions

Many important interactions for simvastatin (Zocor) and atorvastatin relate to drugs that inhibit or induce metabolism via the cytochrome P450 (CYP3A4) enzyme, or that affect transport proteins.

### Starting dose

If co-prescription with a drug that increases systemic exposure to statins is unavoidable, it is particularly important to start on the lowest statin dose. For atorvastatin and simvastatin the starting dose is 10 mg daily.

### Maintenance doses

The table gives important dose restrictions for atorvastatin and simvastatin when used in combination with other drugs. Both drugs interact with grapefruit juice.

**Why not share  
this bulletin with  
your colleagues?**

<b>Interacting drug or food</b>	<b>Simvastatin prescribing advice</b>	<b>Atorvastatin prescribing advice</b>
Potent CYP3A4 inhibitors, including itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, and HIV protease inhibitors	All are contraindicated with simvastatin	Avoid if possible: consider temporary suspension of atorvastatin if interacting drug is taken for short period  <b>Itraconazole:</b> do not exceed 40 mg atorvastatin daily  <b>Clarithromycin:</b> do not exceed 20 mg atorvastatin daily  <b>HIV protease inhibitors:</b> monitor lipid levels to ensure lowest necessary dose of atorvastatin is used
Ciclosporin*	Do not exceed 10 mg simvastatin daily	Do not exceed 10 mg atorvastatin daily
Danazol	Do not exceed 10 mg simvastatin daily	No restriction in Summary of Product Characteristics
Verapamil, amiodarone	Do not exceed 20 mg simvastatin daily	Monitor lipid levels to ensure lowest necessary dose of atorvastatin is used
Diltiazem	Do not exceed 40 mg simvastatin daily	Monitor lipid levels to ensure lowest necessary dose of atorvastatin is used
Grapefruit juice	Avoid grapefruit juice	Limit intake of grapefruit juice to very small quantities (or avoid altogether)
Warfarin/courmarins†	Monitor INR before starting treatment and regularly during treatment, especially with dose changes	Monitor INR before starting treatment and regularly during treatment, especially with dose changes
Fibrates†	Increased risk of myopathy when used with fibrates; do not exceed 10 mg simvastatin daily (except with fenofibrate); gemfibrozil increases systemic exposure to simvastatin	Increased risk of myopathy when used with fibrates; gemfibrozil increases systemic exposure to atorvastatin
Ezetimibe†	Additive risk of myopathy cannot be ruled out	Additive risk of myopathy cannot be ruled out

\*Ciclosporin interacts with all statins and is contraindicated with rosuvastatin—see page 4.

†Warfarin/courmarins, fibrates, and ezetimibe are important potential interactions to consider for all statins—see page 4.

## Medicines that reduce plasma concentrations of simvastatin and atorvastatin

For a Dear Healthcare Professional Letter for atorvastatin sent December 2007, see <http://www.mhra.gov.uk/mhra/HealthcareProfessionalLetters>

Inducers of CYP3A4 (eg, efavirenz, rifampicin, St John's wort) may reduce plasma concentrations of simvastatin and atorvastatin. Colestipol reduces plasma levels of atorvastatin, but lipid-lowering effects may be greater than when either drug is given alone.

## Important interactions to consider with all statins

### *Warfarin/coumarins*

Statins may affect coumarin anticoagulation and increase the risk of haemorrhagic events. Patients who are receiving warfarin should have INR monitoring before starting statins and regularly throughout treatment, especially with statin dose changes. Caution is particularly necessary with fluvastatin (Lescol), which is metabolised by CYP2C9. However, for pravastatin (Lipostat), which is not metabolised by cytochrome P450, warfarin interaction is less of a concern.

### *Fibrates*

For prescribing advice for fibrates, see *Drug Safety Update* 2007; 1(4): 2; [www.mhra.gov.uk/mhra/drugsafetyupdate](http://www.mhra.gov.uk/mhra/drugsafetyupdate)

The use of fibrates alone is occasionally associated with myopathy; use with statins may increase this risk. Furthermore, gemfibrozil increases systemic exposure to simvastatin, atorvastatin, and rosuvastatin (Crestor). Careful monitoring is therefore needed, and maximum daily dose of simvastatin is 10 mg daily when used with fibrates (except fenofibrate). For rosuvastatin, start with 5 mg and do not exceed 20 mg during use with fibrates.

### *Ezetimibe*

Ezetimibe has no pharmacokinetic interaction with statins. However, ezetimibe alone is associated with a risk of myopathy and an additive risk with statins cannot be ruled out.

## Other important interactions with fluvastatin, pravastatin, and rosuvastatin

### *Fluvastatin*

Caution is needed with ciclosporin, fluconazole, phenytoin, and glibenclamide—see product information for details.

### *Rosuvastatin*

Rosuvastatin is not associated with cytochrome P450 interactions. Ciclosporin is contraindicated with rosuvastatin (Crestor). HIV protease inhibitors strongly increase exposure to rosuvastatin (through an unknown mechanism) and are not recommended for combination use. Antacids reduce rosuvastatin plasma levels.

### *Pravastatin*

Pravastatin is not associated with cytochrome P450 interactions. Caution is needed with ciclosporin, erythromycin, and clarithromycin. Cholestyramine and colestipol decrease plasma levels of pravastatin.

## Methylthioninium chloride (methylene blue): CNS toxicity with serotonergic drugs

**Keywords:** encephalopathy, interaction, methylthioninium chloride, methylene blue, neurotoxicity, parathyroidectomy, serotonergic antidepressant, serotonin uptake inhibitor, SSRI

**Methylthioninium chloride (methylene blue) in high intravenous doses should preferably be avoided for patients who are receiving serotonergic drugs (eg, SSRI antidepressants, clomipramine, and venlafaxine)**

Methylthioninium chloride (formerly called methylene blue) is approved for the management of methaemoglobinaemia. It can be given intravenously or by mouth. Methylthioninium can also be of value as a visualising agent in surgical procedures, but it does not have an approved indication for this purpose. During surgery it may be applied locally, but for some procedures it is given intravenously.

We are aware of 27 cases (24 reported in the literature<sup>1-9</sup> and three reported direct to the MHRA) of CNS toxicity when intravenous methylthioninium was used as a visualising agent for parathyroid or thyroid surgery. In all but one case, the patients were also receiving serotonergic drugs (such as SSRI antidepressants, bupropion, buspirone, clomipramine, mirtazapine, and venlafaxine). For parathyroid surgery, methylthioninium chloride has been used in doses of 5–10 mg/kg (typically 7.5 mg/kg),<sup>7,10</sup> which are much higher than the doses used for management of methaemoglobinaemia. However, even doses of 3 mg/kg<sup>9</sup> (and in one case 1.75 mg/kg in a 115-kg woman<sup>8</sup>) have been associated with adverse CNS symptoms.

In the reported cases, CNS toxicity usually came to light within a few hours of parathyroid or thyroid surgery, mostly during recovery from anaesthesia. Confusion and disorientation occurred in most cases and other features included agitation, expressive aphasia, altered muscle tone in limbs, hypoxia, ocular symptoms, and depressed level of consciousness.

### Advice for healthcare professionals:

- The need for intravenous methylthioninium chloride for visualisation in surgical procedures should be assessed carefully: such use should be considered on a case-by-case basis
- Intravenous methylthioninium chloride should preferably be avoided in patients who have been treated recently with drugs that have serotonergic activity
- If use of intravenous methylthioninium chloride cannot be avoided, the minimum possible dose should be used and the patient observed closely for CNS effects for up to 4 hours after administration

- 1 Martindale SJ, Stedeford JC. *Anaesthesia* 2003; **58**: 1041–42.
- 2 Mathew S, et al. *Anaesthesia* 2006; **61**: 580–83.
- 3 Bach KK, et al. *Anesth Analg* 2004; **99**: 1573–74.
- 4 Rosenbaum HK. Malignant Hyperthermia Association of the United States case report, January 2006. See <http://medical.mhaus.org>
- 5 Majithia A, Stearns MP. *J Laryngol Otol* 2006; **120**: 138–40.
- 6 Patel AS, et al. *Head Neck* 2006; **28**: 567–68.
- 7 Kartha SS, et al. *Otolaryngol Head Neck Surg* 2006; **135**: 765–68.
- 8 Mihai R, et al. *Can J Anesth* 2007; **54**: 79–81.
- 9 Sweet G, Standiford SB. *J Am Coll Surg* 2007; **204**: 454–58.
- 10 Rowntree T. *J Roy Soc Med* 1980; **73**: 14–18.

## Desmomelt (desmopressin): call for Yellow Card reporting

**Keywords:** Desmopressin, Desmomelt, removal of indication, primary nocturnal enuresis, bedwetting, nasal spray, melt, hyponatraemia

**Healthcare professionals are encouraged to report all suspected adverse reactions to melt formulations of desmopressin**

Desmopressin is a synthetic analogue of vasopressin. It is indicated for: treatment of primary nocturnal enuresis (PNE); nocturia associated with multiple sclerosis when other treatments have failed; diagnosis and treatment of vasopressin-sensitive cranial diabetes insipidus; establishment of renal concentration capacity; to increase Factor VIII:C and Factor VIII:Ag in patients with mild to moderate haemophilia or von Willebrand's disease who are undergoing surgery or after trauma; and to test for fibrinolytic response.

Desmopressin is available in nasal, oral (tablet or melt), and injection formulations. The PNE indication has been removed from all desmopressin nasal spray products because of an increased risk of hyponatraemia compared with the oral formulation (which remains available for treatment of PNE, along with the melt formulation).

Healthcare professionals should remain vigilant for signs and symptoms of hyponatraemia associated with use of desmopressin, particularly the melt formulation. These may include (in mild cases): anorexia, headache, nausea, or vomiting; or (in more severe cases) muscle cramps and weakness, confusion, convulsions, or coma.

### Reminder for healthcare professionals:

- Nasal formulations of desmopressin should not be used for treatment of PNE
- Healthcare professionals and patients should follow closely the advice on fluid intake in the Summary of Product Characteristics and Patient Information Leaflet to avoid hyponatraemia
- Healthcare professionals are encouraged to report all suspected adverse reactions to melt formulations of desmopressin

See Drug Safety Update 2007; **1** (2): 7.  
[www.mhra.gov.uk/mhra/drugsafetyupdate](http://www.mhra.gov.uk/mhra/drugsafetyupdate)

Complete a Yellow Card: see  
[www.yellowcard.gov.uk](http://www.yellowcard.gov.uk)

## Bivalirudin: risks associated with incorrect dose

**Keywords:** bivalirudin, thrombin inhibitor, percutaneous coronary intervention, PCI, bolus and infusion, major adverse cardiac events, MACE

**Use the approved dose regimen for bivalirudin in percutaneous coronary intervention**

Bivalirudin (Angiox▼) is a direct thrombin inhibitor that is approved for use as an anticoagulant in patients who are undergoing percutaneous coronary intervention (PCI). The approved dose for this indication is a 0.75-mg/kg bolus followed immediately by a 1.75-mg/kg/h infusion for the duration of the intervention.

About 35% of patients entered into a European registry study (enrolled from various countries, but not the UK) received a single bolus or double bolus of bivalirudin without the required maintenance infusion. Most affected patients were recruited in Germany. These non-approved regimens resulted in substantial underdosing and were associated with an increased incidence of major adverse cardiac events (MACE), including cardiac death, myocardial infarction, and urgent revascularisation.

For further information see letter to healthcare professionals sent October 2007.

[http://www.mhra.gov.uk/home/idcplg?IdcService=SS\\_GET\\_PAGE&useSecondary=true&ssDocName=CON2032914&ssTargetNodeId=221](http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2032914&ssTargetNodeId=221)

Healthcare professionals are advised to consult the Summary of Product Characteristics for full prescribing information. See <http://emc.medicines.org.uk/>

### Advice for healthcare professionals:

- The approved dosing regimen for bivalirudin should be used in PCI. Use of a maintenance infusion after an initial bolus is necessary to ensure adequate anticoagulation during PCI.

## Yellow Card scheme update

The Yellow Card scheme collects information on adverse drug reactions in the UK. See [www.yellowcard.gov.uk](http://www.yellowcard.gov.uk)

See [www.gprd.com](http://www.gprd.com)

Access the first Annual Report of ISAC at [http://www.mhra.gov.uk/home/idcplg?IdcService=SS\\_GET\\_PAGE&nodel=1171](http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodel=1171)

Read more about ISAC, including meeting minutes and full Committee membership, at [http://www.mhra.gov.uk/home/idcplg?IdcService=SS\\_GET\\_PAGE&nodel=929](http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodel=929)

Queries about the use of Yellow Card data can be sent to [isacyellowcarddata@mhra.gsi.gov.uk](mailto:isacyellowcarddata@mhra.gsi.gov.uk)

### What happens to Yellow Card data?

The Yellow Card scheme collects information on adverse drug reactions in the UK and is therefore a potentially important source of information for researchers. A 2004 Report of an Independent Review of Access to the Yellow Card Scheme (London: The Stationary Office) by Dr Jeremy Metters recommended the widening of access to Yellow Card data.

The Independent Scientific Advisory Committee (ISAC) is a non-statutory expert advisory body that was established in 2006 by the Secretary of State. ISAC's remit is to consider, and give advice to the MHRA on, applications for Yellow Card data that fall outside the scope of the Freedom of Information Act. ISAC also considers and advises on all projects that propose to use data from the General Practice Research Database (GPRD).

ISAC can give advice on wider aspects of the use of Yellow Card or GPRD data (eg, safe disposal of electronic data), and on the relevance of seeking ethics review for a proposal from the NHS Research Ethics Committee.

The Chair of ISAC is Professor Jennifer Adgey (Honorary Professor of Cardiology, Queens University, Belfast; and Honorary Consultant, Cardiology, Royal Victoria Hospital, Belfast), who is supported by nine members with clinical and statistical expertise; there are also two lay members. Professor Adgey took over as Chair from Dr Brian Gennery (former Director of Clinical Research, University of Surrey) on Jan 1, 2008.

In ISAC's first year, it met five times and reviewed four new applications to use Yellow Card data. The Committee also considered some applications for which further information had been requested by the predecessor to ISAC, the Interim Committee on Yellow Card data. For research proposals using Yellow Card data, ISAC considers the method of study; its appropriateness; the implications of the Freedom of Information Act and Data Protection Act on data release; and how use of other data would interact with Yellow Card data.

In its first year, ISAC approved three research applications that proposed to use Yellow Card data: acute renal toxicity and its detection by the Yellow Card Scheme (Professor Nick Bateman, University of Edinburgh); pharmacogenetics of antimicrobial drug-induced liver injury (Professor Munir Pirmohammed, University of Liverpool); and European case-control collection of selected adverse drug reactions (Dr Miriam Molokhia, London School of Hygiene and Tropical Medicine).

We encourage researchers to apply to use valuable data from the Yellow Card scheme to help studies that aim to advance knowledge in the safe use of medicines.

# Hot topic

**Long-acting  $\beta_2$  agonists should be prescribed for the treatment of moderate to severe asthma only in conjunction with inhaled corticosteroids. When appropriate, these medicines should be prescribed in a combination inhaler**

## Long-acting $\beta_2$ agonists for asthma: review

The MHRA has reviewed the use of long-acting  $\beta_2$  agonists (LABA) in the treatment of asthma after concerns raised by the Salmeterol Multicenter Asthma Research Trial (SMART).<sup>1</sup>

This double-blind randomised placebo-controlled trial recorded more respiratory-related deaths, asthma-related deaths, and combined asthma-related deaths or life-threatening experiences in the salmeterol group than in the placebo group.

The MHRA has reviewed: the pharmacology of the two currently available LABA—salmeterol (Serevent) and formoterol (Atimos Modulite▼, Foradil, Oxis), and the combination products Seretide and Symbicort; the current position of research into the  $\beta_2$  adrenoreceptor genotype; the epidemiology of asthma in relation to the introduction of LABA; and an overall assessment of the benefits and risks of LABA in the treatment of asthma.

The conclusions from the review are:

- Epidemiological data show that since the introduction of LABA, there has been a decrease in asthma-related hospitalisations in adolescents and a decrease in asthma-related mortality in all ages
- Data from randomised controlled clinical trials do not suggest a similar safety concern to that shown in postmarketing studies, probably because of more-consistent use of concomitant inhaled corticosteroids in randomised controlled settings. The data support the use of LABA in conjunction with inhaled corticosteroids in the treatment of moderate to severe asthma consistent with the guideline on the management of asthma from the British Thoracic Society and Scottish Intercollegiate Guidelines Network
- To aid compliance with the concomitant use of inhaled corticosteroids and LABA, a combination inhaler should be used when appropriate

Further epidemiological studies are under way to assess the relation between adverse outcomes and use of LABA, the results of which are expected before the end of 2008. The MHRA is also reviewing of the role of LABA in the treatment of asthma in children younger than age 12 years.

Further information about LABA in asthma management is available on our website.

1 Nelson HS, et al. *Chest* 2006; **129**: 15–26.

Access the guideline on the management of asthma at <http://www.sign.ac.uk/guidelines/fulltext/63/index.html>

For further information from the MHRA, see [http://www.mhra.gov.uk/home/idcplg?IdcService=SS\\_GET\\_PAG&nodeId=1016](http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAG&nodeId=1016)

## Stop press

### Carisoprodol: recommendation to suspend Marketing Authorisations

For further information, see [http://www.emea.europa.eu/pdfs/human/press/pr/Pressrelease\\_Carisoprodol\\_52046307en.pdf](http://www.emea.europa.eu/pdfs/human/press/pr/Pressrelease_Carisoprodol_52046307en.pdf) and [http://www.emea.europa.eu/pdfs/human/press/pr/Carisoprodol\\_Q&A\\_52014007en.pdf](http://www.emea.europa.eu/pdfs/human/press/pr/Carisoprodol_Q&A_52014007en.pdf)

The European Medicines Agency (EMA) has reviewed the safety of carisoprodol (Carisoma), a treatment for short-term symptomatic relief of muscle spasm. The Committee for Medicinal Products for Human Use (CHMP) concluded that there was a risk of abuse, addiction, intoxication, and psychomotor impairment, and that there are effective alternatives with a more favourable safety profile. The EMA has therefore recommended suspension of the Marketing Authorisation (MA) for all carisoprodol-containing products.

The MHRA is working with the UK MA holder (Forest Laboratories UK Ltd) to achieve a planned withdrawal of this product from the market. Patients are reminded to consult their doctor or pharmacist, and not to seek supplies of carisoprodol from other sources.

### Paraffin-based treatments: risk of fire hazard

Paraffin-based products such as white soft paraffin, white soft paraffin plus 50% liquid paraffin, or emulsifying ointment that have contact with dressings and clothing are ignited easily by a naked flame. This risk will be greater when these preparations are applied to large areas of the body, and when clothing or dressings become soaked with the ointment.

See <http://www.npsa.nhs.uk>

The National Patient Safety Agency (NPSA) is aware of a fatal incident reported to the National Reporting & Learning System, in which a paraffin-based skin product that was in contact with a patient's dressings and clothing was ignited by a naked flame. The NPSA is disseminating information to clinical staff to ensure patients and carers are made aware of the risks.

See <http://www.bnf.org>

The September 2007 edition of British National Formulary includes a new warning about the risk of fire associated with paraffin-based emollients.

### Oral anticancer medicines: risk of incorrect dosing

See [www.npsa.nhs.uk](http://www.npsa.nhs.uk)

The NPSA is alerting all healthcare professionals who use oral anticancer medicines about potentially fatal outcomes if incorrect doses are prescribed, dispensed, or administered. Risks are increased if healthcare practitioners who are not cancer specialists prescribe, dispense, or administer these medicines.

NPSA is issuing guidance to all clinical staff that the prescribing, dispensing, and administering of oral anticancer medicine should be carried out and monitored to the same standard as that for injected cancer therapy.

## Other information from the MHRA

### Patient Information Leaflet of the month

New legal requirements on manufacturers require them to test Patient Information Leaflets (PILs) with potential patients. User-testing makes sure that the presentation of the information enables patients to find and understand key messages for safe and effective use of the medicine. To promote this new initiative, we are publishing a series of examples of best practice on our website. The latest in this series is the PIL for **Crestor** (rosuvastatin, an oral statin for hypercholesterolaemia—see also page 2).

Access PIL of the month at [http://www.mhra.gov.uk/home/idcplg?IdcService=GET\\_FILE&dDocName=con2032612&RevisionSelectionMethod=Latest](http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=con2032612&RevisionSelectionMethod=Latest)

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