Drug Safety Update

MHRA

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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Contents

Click on text to go to page

We have recently completed a risk-benefit review of orciprenaline sulphate, a non-selective β-agonist that has been licensed since 1972 for treatment of reversible airways obstruction and is currently available for oral administration as a syrup. An analysis of the evidence for this product has shown that the balance of benefits and risks is no longer favourable. Therefore, orciprenaline sulphate is to be withdrawn from the market over the next year—see p 6 for further information.

Also this month, we bring you news of the conclusion of a Europe-wide review of the safety of bisphosphonates and the risk of jaw osteonecrosis. Page 2 brings you key messages for healthcare professionals from this review.

Finally, our Yellow Card Scheme update this month brings you news on how to report suspected adverse reactions to all flu vaccines (ie, both for seasonal flu and swine flu) via our dedicated portal (p 7). We also feed back on suspected adverse drug reactions we have received for the antiviral medicines in use during the pandemic. Such reporting via our portal at www.mhra.gov.uk/swineflu is vital to our continual safety monitoring of these flu medicines and vaccines.

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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

Bisphosphonates: osteonecrosis of the jaw

Keywords: bisphosphonates, osteoporosis, Paget's disease, jaw osteonecrosis, cancer

The risk of osteonecrosis of the jaw is greater for patients receiving intravenous bisphosphonates for cancer than for patients receiving oral bisphosphonates for osteoporosis or Paget's disease. All patients with cancer should have a dental check-up before bisphosphonate treatment. During treatment, patients should be encouraged to: maintain good oral hygiene; receive routine dental check-ups; and report any oral symptoms such as dental mobility, pain, or swelling

A patient may be considered to have ONJ related to bisphosphonates if all of the following three characteristics are present:

1 Exposed or necrotic bone in the maxillofacial region that has persisted for more than 8 weeks
2 No history of irradiation of the jaw
3 Current or previous treatment with a bisphosphonate.

For further information from the EMEA, see
http://www.emea.europa.eu/pdfs/human/opinion/Q&A_Bisphosphonates_29247509en.pdf
and
http://www.emea.europa.eu/htms/human/opiniongen/list.htm

Individual bisphosphonates have different indications, and are used for: prophylaxis and treatment of osteoporosis; treatment of Paget's disease; and as part of some cancer regimens, particularly for metastatic bone cancer and multiple myeloma.

A Europe-wide review has been completed on the risk of osteonecrosis of the jaw (ONJ) in association with the use of bisphosphonates. The review included data from the published literature and data provided by the Marketing Authorisation Holders (including data from experimental and preclinical studies, clinical trials, and post-marketing reports) and guidelines produced by learned societies. The review also incorporated advice from a group of experts representing all areas of medicine where bisphosphonates are used, dentistry and bone surgery, and representatives of patients' organisations.

Up to Oct 26, 2009, the majority of UK Yellow Card reports of ONJ have been in patients treated with zoledronate (172 reports). Yellow Card reports of ONJ have also been received in association with alendronate (47 reports), pamidronate (38 reports), ibandronate (28 reports), clodronate (12 reports), and risedronate (11 reports). It is very important to remember that the number of reports for a particular bisphosphonate cannot be used to determine the incidence of ONJ for each individual drug because neither the total number of reactions occurring nor the number of patients using the drug is known.

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) reached conclusions on the currently available evidence on four main areas: definition and diagnosis of ONJ related to bisphosphonates; possible underlying pathophysiological mechanism(s); risk stratification; and risk minimisation. The key messages for healthcare professionals from this review are given below.

Advice for healthcare professionals:

- The risk of developing ONJ in association with oral bisphosphonates seems to be low. The risk of ONJ is substantially greater for patients receiving intravenous bisphosphonates for cancer indications than for patients receiving oral bisphosphonates for osteoporosis or Paget's disease
- There is clear evidence to suggest bisphosphonate-specific and indication-specific risk factors such as potency (highest for zoledronate); route of administration (eg, intravenous ibandronte, pamidronate, and zoledronate); and cumulative dose. The evidence base is less robust for other proposed risk factors (eg, duration and type of malignant disease,

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See EMEA assessment report for a discussion of these possible risk factors http://www.emea.europa.eu/htms/human/opiniongen/list.htm

concomitant treatment, smoking, and comorbid conditions). However, healthcare professionals should consider these risk factors when evaluating an individual's risk of developing ONJ

- A history of dental disease—including invasive dental procedures, dental trauma, periodontal disease, and poorly fitting dentures—is associated with an increased risk of ONJ

Risk minimisation

- All patients with cancer should have a dental check-up before bisphosphonate treatment. All other patients who start bisphosphonates should have a dental examination only if they have poor dental status
- During bisphosphonate treatment, patients should maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain, or swelling

The risk of ONJ with bisphosphonates will be kept under close review in Europe. Further research is needed to increase knowledge about the underlying mechanisms and risk factors for ONJ, and about how best to minimise these risks. The EU regulatory authorities will explore strategies to promote this research, and the CHMP has adopted a definition (see margin note, p 2) of ONJ related to bisphosphonates to facilitate future case reporting and research.

For details of an ongoing national study on bisphosphonate-induced jaw osteonecrosis, see http://www.ingentaconnect.com/content/rcse/brcs/2009/00000091/00000008/art00007 (accessed Oct 20, 2009).

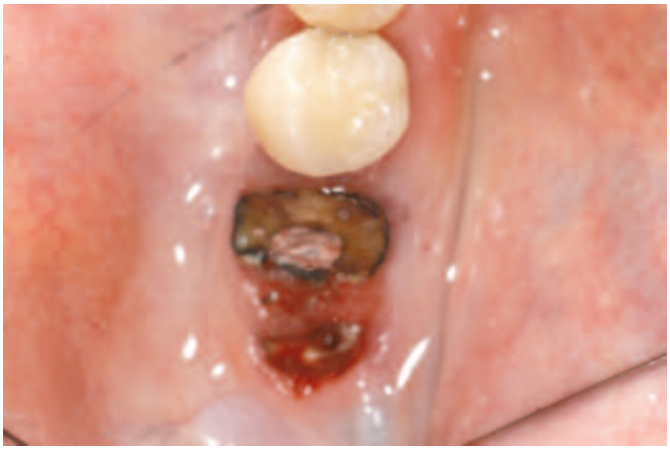


Image credit: John W Hellstein, University of Iowa College of Dentistry and Hardin MD, University of Iowa. See http://www.lib.uiowa.edu/HARDIN/md/ui/dent/osteonecrosis1.html (accessed Oct 6, 2009).

Osteonecrosis of the jaw

Vigabatrin for infantile spasms: risk of movement disorders and MRI abnormalities

Keywords: vigabatrin, Sabril, antiepileptic, movement disorders, MRI abnormalities

Movement disorders have been reported in patients treated with vigabatrin for infantile spasms. If new movement disorders occur during treatment with vigabatrin, consideration should be given to dose reduction or a gradual discontinuation of treatment in consultation with specialist advice

Vigabatrin (Sabril) is an antiepileptic indicated, in combination with other antiepileptic drugs, for the treatment of patients with resistant partial epilepsy (with or without secondary generalisation) who have not responded to, or who are intolerant to, all other appropriate drug combinations. Vigabatrin is also indicated as monotherapy in the treatment of infantile spasms (West's syndrome).

Researchers in Finland first raised concerns about a risk of movement disorders (including dystonia, dyskinesia, and hypertonia) and brain abnormalities on MRI (interpreted as cytotoxic oedema) associated with the use of vigabatrin, after they received reports of these adverse drug reactions from a Finnish healthcare professional.

A Europe-wide review completed in July 2009 involving experts in paediatric neurology from the UK assessed the evidence available on this issue, including preclinical data, clinical data, reported cases of adverse drug reactions, and relevant published literature.

Clinical trial data[1] for vigabatrin in infantile spasms provide evidence of brain MRI abnormalities at all doses, but in particular in young infants treated with high doses (≥125 mg/kg/day). These MRI abnormalities were transient, seemed to be dose dependent, and in most patients resolved even if treatment with vigabatrin continued.

The review concluded that it is not possible to correlate the MRI findings with the movement disorders based on the current data. Therefore, the two events of movement disorders and brain MRI abnormalities will be independently described in the updated product information for vigabatrin to reflect these new data. The risk of movement disorders and brain MRI abnormalities with vigabatrin will be kept under close review by EU regulatory authorities, including the MHRA.

1 Wheless J, et al. *Epilepsia* 2009; **50:** 195–205.

Further information is available in an assessment report on this topic at http://www.mhra.gov.uk/safetyinformation/generalsafetyinformationandadvice/product-specificinformationandadvice/antiepileptics/index.htm

Advice for healthcare professionals:

- Cases of abnormal brain MRI findings have been reported, in particular in young infants treated for infantile spasms with high doses (≥125 mg/kg/day) of vigabatrin. The clinical significance of these findings is currently unknown
- Movement disorders including dystonia, dyskinesia, and hypertonia have been reported in patients treated for infantile spasms. The balance of benefits and risks of vigabatrin should be evaluated on an individual patient basis. If new movement disorders occur during treatment with vigabatrin, consideration should be given to dose reduction or a gradual discontinuation of treatment in consultation with specialist advice
- Please report suspected adverse reactions to medicines even if you cannot be sure that there is a causal association (see www.yellowcard.gov.uk)

Colchicine: reminder on risk of serious and fatal toxicity in overdose

Keywords: Colchicine, gout, overdose, toxicity

Colchicine is extremely toxic in overdose

Colchicine is licensed for the treatment of acute gout, but only in cases where non-steroidal anti-inflammatory drugs are not tolerated or ineffective. It is also licensed for short-term prophylaxis during initial therapy with other drug treatments.

The MHRA is aware of a number of serious and fatal reports involving colchicine overdose. Colchicine has a narrow therapeutic window and is extremely toxic in overdose. Patients at particular risk of toxicity are those with renal or hepatic impairment, gastrointestinal or cardiac disease, and patients at extremes of age. Colchicine overdose is complex and specialist advice should be promptly obtained. There is often a delay of up to 6 hours before toxicity is apparent, and some features of toxicity may be delayed by 1 week or longer. All patients, even in the absence of early symptoms, should be referred for immediate medical assessment.

Symptoms of colchicine overdose

Early features (up to 1 day after ingestion) include nausea, vomiting, abdominal pain, and diarrhoea. Diarrhoea may be profuse and bloody, and the patient may present with electrolyte disturbances and hypovolaemic shock.

Features after 1–7 days include confusion, decreased cardiac output, cardiac arrhythmias, renal and hepatic impairment, respiratory distress, hyperpyrexia, and bone-marrow depression. This can progress in severe cases to include multiple organ failure with accompanying bone-marrow aplasia, convulsions, coma, rhabdomyolysis, and disseminated intravascular coagulation.

Key points in the initial management of colchicine overdose

Consider oral activated charcoal in adults who have ingested more than 0·1 mg/kg bodyweight over a period of 1 hour, or in children who have ingested any amount over a period of 1 hour. Further doses of activated charcoal may enhance systemic elimination and may be considered in patients who have ingested more than 0·3 mg/kg.

Neither haemodialysis nor haemoperfusion enhance colchicine elimination.

Management should include general symptomatic and supportive measures as indicated by the patient's clinical condition, including monitoring of vital signs, electrocardiography, and haematological and biochemical indices.

To allow for the delayed onset of symptoms, patients should be carefully monitored for at least 6 hours after ingestion, or for at least 12 hours if they have taken more than 0·3 mg/kg. After this time, asymptomatic patients may be discharged with advice to return if gastrointestinal symptoms appear.

Advice for healthcare professionals:

- Colchicine has a narrow therapeutic window and is extremely toxic in overdose
- Patients at particular risk of toxicity are those with renal or hepatic impairment, gastrointestinal or cardiac disease, and patients at extremes of age
- The symptoms of overdose are often delayed
- All patients, even in the absence of early symptoms, should be referred for immediate medical assessment

See www.toxbase.org

Further information on the presentation and management of colchicine overdose is available from TOXBASE, the clinical toxicology database of the National Poisons Information Service (NPIS).

Orciprenaline sulphate (Alupent): withdrawal due to unfavourable benefit-risk profile

Keywords: orciprenaline sulphate, Alupent syrup, non-specific β-agonist, reversible airways obstruction, asthma

Orciprenaline sulphate is to be withdrawn over the next year because a review has concluded that the benefit-risk profile is unfavourable. Patients who require a liquid oral formulation of a β-agonist should be switched to a more-selective short-acting β_2-agonist such as salbutamol or terbutaline

Orciprenaline sulphate (Alupent) is a non-specific β-agonist indicated for reversible airways obstruction and suggested for maintenance therapy. It is currently available for oral administration as a syrup.

See
Wolfe JD, et al. *Pediatrics* 1991; **88:** 312–19.

Further information is available in an assessment report on this topic at http://www.mhra.gov.uk/safetyinformation/safetywarningsalertsandrecalls/safetywarningsandmessagesformedicines/index.htm

An analysis of the available literature demonstrated that orciprenaline sulphate is significantly less efficacious than salbutamol in terms of both the extent and duration of bronchodilation. Yellow Card reports and clinical trial data show a significantly increased incidence of cardiac side effects, mainly palpitations and tachycardia because of its non-selectivity. Importantly, clinical trial data show that cardiac side effects occur before maximum bronchodilation is achieved because of its non-selectivity.

Accordingly, the Commission on Human Medicines (CHM) has advised that the balance of benefit and risks for orciprenaline sulphate is no longer favourable and concluded that:

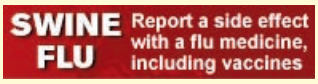
- there should be a planned withdrawal of orciprenaline sulphate from the UK market
- there are no patient groups for whom transfer to a more-selective β_2-agonist would be inappropriate

The MHRA is working with the manufacturer to achieve a planned voluntary withdrawal of orciprenaline sulphate over the next year. The product will continue to be available for several months, but it is recommended that patients are switched to a more-selective β_2-agonist at the earliest opportunity.

Advice for healthcare professionals:

- Orciprenaline sulphate is to be withdrawn from the UK market over the next year
- Patients who require a liquid oral formulation of a β-agonist should be switched to a more-selective short-acting β_2-agonist such as salbutamol or terbutaline

Yellow Card Scheme update



MHRA Swine Flu ADR Portal now extended to include reporting for all flu vaccines

In July 2009, we launched a special web-based system for reporting suspected adverse drug reactions (ADRs) to oseltamivir (Tamiflu) and zanamivir (Relenza)—the **Swine Flu ADR Portal**. Since then we have received an extremely encouraging level of reporting (see below), so thank you for helping us safeguard public health.

As we enter the next pandemic wave, we continue to need your help in monitoring the safety of not only oseltamivir and zanamivir, but also the new swine flu vaccines: please report to us all suspected adverse reactions to these medicines and vaccines. You can do this now via the Swine Flu ADR Portal at www.mhra.gov.uk/swineflu.

It is likely that many patients who receive one of the new swine flu vaccines will also receive a seasonal flu vaccine around the same time. For this reason, we have extended the Swine Flu ADR Portal to include reporting for all flu vaccines (ie, both seasonal and swine flu).

How to report a suspected adverse reaction to pandemic antivirals and flu vaccines

- Please report suspected ADRs to oseltamivir, zanamivir, and all flu vaccines (seasonal and swine flu) via the Swine Flu ADR Portal at www.mhra.gov.uk/swineflu
- Please remember to include the following important information in your report, if possible:
  - the patient's age
  - a concise description of the suspected adverse reaction and outcome
  - information on any underlying risk factors for the adverse reaction or for flu complications; or state if there are no known risk factors
  - any other information about the patient or additional clinical details which will help us in our assessment of the case

In addition, for the new swine flu vaccines, please also provide:

- the brand name (Celvapan or Pandemrix)
- batch number(s)
- dates of administration of first and second doses (if applicable)
- the reason for vaccination (eg, patient is in seasonal flu at-risk group—please specify; is pregnant; is a close contact of immunocompromised; or is a healthcare worker)
- the arm in which the vaccine was given (important if seasonal flu vaccine was administered at the same time)

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Yellow Card Scheme update *Cont.*

Green Book:
http://www.dh.gov.uk/en/Publichealth/Healthprotection/Immunisation/Greenbook/dh_4097254

- Reporting anaphylaxis and allergic reactions:

  Anaphylaxis is an acute, severe allergic reaction that is a very rare, recognised side-effect of most vaccines. Suspected cases should be reported via the Swine Flu ADR portal. Chapter 8 of the Green Book gives detailed guidance on distinguishing between faints, panic attacks, and the clinical features of anaphylaxis.

  If a case of suspected anaphylaxis meets diagnostic criteria, please report it via the Swine Flu ADR portal as a case of 'anaphylaxis' (or if appropriate 'anaphylactoid reaction'). Cases of less-severe allergic reactions (ie, those that do not have the full clinical features of anaphylaxis) should be reported as 'allergic reaction', not 'anaphylaxis'. Any relevant signs or symptoms should be reported in the 'additional information' section

- You do not have to have all the information available to report, and you do not need to be sure that the antiviral or vaccine caused the adverse event—if in doubt please report

- The existing Yellow Card Scheme will remain in operation during the pandemic for reporting suspected adverse reactions to all other medicines and vaccines

We recognise that this is an extremely busy time for healthcare professionals and we appreciate your extra effort and time taken to report. Every report matters.

Suspected ADRs to oseltamivir and zanamivir received

Between April 1, 2009 and Oct 22, 2009, the MHRA has received 850 reports of suspected ADRs for oseltamivir and 20 reports for zanamivir.

Oseltamivir

The 850 reports received between April 1, 2009 and Oct 22, 2009 include 1489 suspected adverse reactions.

The most commonly reported suspected ADRs are consistent with the signs and symptoms of recognised side effects such as mild allergic reactions, gastrointestinal events, headache, and dizziness which can also be caused by flu-like illness.

For further information see
www.mhra.gov.uk/swineflu

We have received seven reports in which the patient died after oseltamivir treatment. These cases have been fully evaluated and in none of these is there evidence to confirm that oseltamivir was directly responsible for the fatal event.

Closely monitored adverse events

Neuropsychiatric adverse reactions, including convulsions and delirium (with symptoms such as confusion, abnormal behaviour, hallucinations, agitation, anxiety, and nightmares); and serious skin reactions including Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are listed as possible side effects in the product information for oseltamivir. We have received a number of reports of these types of reactions; however, flu itself can be associated with various neurological and behavioural symptoms, sometimes without obvious signs of a severe infection, and serious skin reactions such as SJS and TEN can also be caused by viral infections.

We also continue to keep under review reports suggesting a possible drug interaction between oseltamivir and warfarin, resulting in prolonged blood clotting

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Yellow Card Scheme update *Cont.*

time. Infection and associated symptoms (eg, decreased appetite and anorexia) can affect blood-clotting control. Therefore it is very difficult to establish whether these cases represent a true drug interaction. Currently, there is no strong evidence of an interaction between the two drugs. Patients should continue to take oseltamivir and warfarin as advised by their healthcare provider.

Zanamivir

The 20 reports received for zanamivir between April 1, 2009 and Oct 22, 2009 include 39 suspected adverse reactions.

Most of the reported suspected ADRs are consistent with the signs and symptoms of known side effects such as allergic reactions and bronchospasm. Most other reported events (such as diarrhoea, nausea, vomiting, fatigue, headache and dizziness) can be caused by flu-like illness.

There has been a case of intrauterine death after exposure during pregnancy. However, currently there is no evidence to suggest that zanamivir (or oseltamivir) carries any risks (maternal, fetal, perinatal, or postnatal) during pregnancy. A recent review of available evidence by European regulatory authorities led to a recommendation that because of the potentially serious risks of H1N1 swine flu in pregnancy, the benefits of using zanamivir (or oseltamivir) in treating flu in pregnant or breastfeeding women outweigh any known risks.

The balance of risks and benefits for both osetamivir and zanamivir within their licensed indications remain positive.

Don't forget: If you suspect that a flu antiviral or vaccination may have caused an adverse reaction, please don't delay and report it to us via www.mhra.gov.uk/swineflu

MHRA collaboration with UK Teratology Information Service: reporting side effects to antivirals in pregnant women

The UK Teratology Information Service (UKTIS) has been commissioned by the National Institute for Health Research to carry out a research project during the current swine flu outbreak to learn more about the effects of swine flu and its treatments in pregnancy for both the mother and baby. The MHRA is collaborating with UKTIS on this study.

UKTIS is seeking women to participate in the research who are pregnant and either

- have had symptoms of flu, or
- have been in contact with flu virus and are being offered antiviral treatment, whether or not they decide to take these

To advise of eligible cases or obtain more information about the study, please contact UKTIS on the Swine Flu Study Line 0191 2606197 or visit the UKTIS website: http://www.uktis.org

Reporting side effects to antivirals during pregnancy

We would encourage healthcare professionals and members of the public to consider reporting directly to UKTIS all suspected side effects to oseltamivir or zanamivir that occur after use during pregnancy. Participation in the study is voluntary, however, and if you prefer, you can still report directly to MHRA via the Swine Flu ADR portal.

Hot topic

This Hot topic informs you of changes to the legislation on the mixing of medicines in clinical practice

Medical and non-medical prescribing: mixing medicines in clinical practice

Under current legislation, except in very restricted circumstances, mixing drugs together, where one is not a vehicle for the administration of the other, creates an unlicensed medicine. The person undertaking this preparation, unless an exemption applies, must hold a manufacturer's licence.

Background: mixing of medicines in palliative care

In palliative care, it is usual to mix two or more medicines in a syringe driver before administration. In 2008, the MHRA realised that the legal position could potentially obstruct the provision of effective pain relief and symptom control to patients receiving palliative care. As a holding measure, we issued a statement that enforcement action would not be taken for breaches of medicines legislation by independent prescribers and nurses in palliative care who were engaged in mixing medicines, unless it would be in the public interest to do so.

Public consultation

To regularise the position permanently, we sought the Commission on Human Medicine's (CHM) views on a public consultation proposing changes to legislation. CHM considered several options for change and provisionally favoured an amendment enabling non-medical prescribers to order "specially prepared" products for their individual patients, and to enable non-prescriber nurses or pharmacists to mix those medicines before administration. We began the consultation on this basis in December 2008.

In the meantime, a CHM Working Group was established to discuss the proposals and consider the results of the consultation; external experts were invited to offer views and advice. It became clear to the Working Group that "mixing" was not restricted to palliative care and that any legislative amendment which only addressed this area would not meet current clinical need.

A summary of the report can be accessed here: http://www.mhra.gov.uk/Howweregulate/Medicines/Availabilityprescribingsellingandsupplyingofmedicines/Frequentlyraisedissues/Palliativecare/index.htm

Latest information on mixing of medicines in clinical practice

In May 2009, CHM considered a report from the Working Group. The Group recommended that:

- Doctors and dentists (who can already mix medicines) should be able to direct others to mix
- Non-medical prescribers should be able to mix medicines and direct others to mix
- Nurse and pharmacist independent prescribers should be allowed to prescribe unlicensed medicines for their patients
- The MHRA should approach the Home Office with CHM's recommendations to make corresponding amendments to the Misuse of Drugs Regulations
- Guidance should be developed for those involved in the "mixing" of medicines
- Research should be commissioned to develop authoritative national advice on "mixing" of medicines

The MHRA plans to implement the necessary legislative amendments in November 2009.

The National Prescribing Centre will be producing a short good-practice guide to support practice in the mixing of medicines post-legislation. Further details will be available from www.npc.co.uk

Hot topic

Statins: updated product information in patient leaflets on adverse reactions

New product information will shortly be coming into the packs of all statins (HMG-CoA reductase inhibitors: simvastatin, atorvastatin, pravastatin, fluvastatin, and rosuvastatin).

See Drug Safety Update, February 2009, p 2; www.mhra.gov.uk/mhra/drugsafetyupdate

In February 2008, we reported a European-wide review on statins. New advice and information on side effects have been agreed, and healthcare professionals should be aware of the updated information so they can discuss it appropriately with new and existing patients.

The headline message from the review was that the balance of risks and benefits of statins as a class remains positive. Statins are one of the most important and widely used medicines in patients with lipid disorders and in the prevention of cardiovascular events. The efficacy and safety of statins have been studied in a number of large trials for both primary and secondary prevention of cardiovascular disease showing that overall, statins can reduce heart attacks and the need for bypass surgery and similar types of operation, and even save lives for certain patient groups. Trials have also shown that statins are generally well tolerated by most people who use them.

However, the review also identified the need for the product information for all statins to reflect the issues identified from analyses of clinical trial and post-marketing data from case reports of adverse drug reactions. These included sleep disturbance, memory loss, sexual disturbances, depression, and interstitial pneumopathy. The review also considered published and unpublished data and relevant clinical guidelines, and concluded that it was important that prescribers and patients alike are aware of the potential for these adverse reactions.

- Patients should be made aware that treatment with any statin may be associated with depression, sleep disturbances, memory loss and sexual dysfunction
- Statins may very rarely be associated with interstitial lung disease. Patients should seek help from their doctor if they develop presenting features of interstitial lung disease such as dyspnoea, non-productive cough, and deterioration in general health (eg, fatigue, weight loss, and fever)

On the basis of the data examined for individual statins and the class as a whole, the review concluded that there is sufficient evidence to support a possible causal relationship between statin use and the above adverse reactions. Summaries of Product Characteristics and Patient Information Leaflets are being amended to include the potential for these reactions.

See also Patient Information Leaflet of the month, p 12

Prescribers will wish to be aware of these changes coming through so that they can discuss them with patients.

Stop press

Oseltamivir (Tamiflu): update to Patient Information Leaflet

We are updating the UK versions of the Patient Information Leaflet for **oseltamivir (Tamiflu)** to clarify the advice relating to aspirin use during treatment with Tamiflu. The Patient Information Leaflets, including those with the 30/45 mg paediatric formulations, stated that "Tamiflu can be taken with paracetamol, ibuprofen, or acetylsalicylic acid (aspirin)". This reflects the fact that there is no known interaction between oseltamivir and aspirin. It must not be interpreted that aspirin can be given to anyone younger than 16 years with Tamiflu. The use of aspirin is, and remains, contraindicated under 16 years because of the risk of Reye's syndrome.

Further information is available at www.mhra.gov.uk/swineflu

Other information from the MHRA

Patient Information Leaflet of the month: Zocor Heart-Pro

Examples of leaflets in this feature can be found at: http://www.mhra.gov.uk/Howweregulate/Medicines/Labelspatientinformationleafletsandpackaging/Patientinformationleaflet(PIL)ofthemonth/index.htm

Patient information leaflets (PILs) are improving in quality as a result of new legal obligations on manufacturers to test the documents on potential patients. Testing makes sure that the presentation of the information enables patients to find and understand key messages for safe use about the medicine within the PIL and thereby enables them to use the medicine safely and effectively. To promote this new initiative, we are publishing a series of examples of best practice on our website. The latest in the series is for **Zocor Heart-Pro**, a **simvastatin**-containing medicine, and includes the updated safety information announced in this edition (p 11).

Introduction of the Traditional Herbal Registration Certification Mark

A number of herbal products have now been registered under the Traditional Herbal Registration (THR) scheme, which shows that they meet the required standards of quality, safety, and evidence of traditional use. Some of these products are starting to appear on the market, with many more expected in the coming months and years.

All THR products have a nine-digit registration number starting with the letters THR on the product container or packaging. To help consumers more easily distinguish those products benefiting from a THR from those which do not, a Certification Mark has been designed and launched as an additional visible symbol.

Read more about the THR Certification Mark at www.mhra.gov.uk/thr

Read more about the Commission on Human Medicines, including summaries of minutes from meetings, at www.mhra.gov.uk/Committees/Medicinesadvisorybodies/CommissiononHumanMedicines

Sign up to receive an email alert when a new issue is published: email registration@mhradrugsafety.org.uk

Report a suspected adverse drug reaction at www.yellowcard.gov.uk