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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Our first issue of volume 3 of Drug Safety Update brings you a selection of hot topics in drug safety. Firstly, we have a safety overview of the antivirals oseltamivir (Tamiflu) and zanamivir (Relenza)—two important medicines for use in the current swine flu pandemic (p 2). You can find out more about the MHRA's role in safeguarding public health during the spread of swine flu at http://www.mhra.gov.uk/swineflu

We remain committed to providing information on the safer use of herbal products: p 5 highlights sources of safety information for herbal remedies. Please remember to report suspected adverse reactions to any herbal product on a Yellow Card at www.yellowcard.gov.uk

We are also committed to monitoring the effect of the actions we take on medicines to ensure that we effectively safeguard public health. P 7 explains the collaborative work we engage in to help ensure that our decisions have a positive outcome for patients and the public.

As Drug Safety Update enters its third year, we hope you continue to read the bulletin for its essential current prescribing information to support your practice.

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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.

Yellow Card Scheme update

The Yellow Card Scheme collects information on suspected adverse drug reactions in the UK. See www.yellowcard.gov.uk

For information about the Yellow Card Scheme, be sure to read our Hot topics on:

- the safety profiles of zanamivir (Relenza) and oseltamivir (Tamiflu), including information on how to report a suspected adverse drug reaction with these antiviral medicines using our dedicated online portal at www.mhra.gov.uk/swineflu (p 2, below)
- the safety of herbal remedies, which includes details of how you can report suspected adverse reactions to herbal products on a Yellow Card (p 6)

Hot topic

The UK has stockpiled the antiviral medicines oseltamivir (Tamiflu) and zanamivir (Relenza) for the management of the swine influenza A/H1N1 pandemic. As use of these products will increase in the coming weeks and months, this article outlines some of the key facts on their safe use.

Stay up to date on the latest information from the MHRA via www.mhra.gov.uk/swineflu

Further information about these medicines, including a list of known side effects, can be found in the Summary of Product Characteristics and Patient Information Leaflet at www.emc.medicines.org.uk

Safety information on oseltamivir (Tamiflu) and zanamivir (Relenza) for pandemic swine influenza A/H1N1

Tamiflu and Relenza are both neuraminidase enzyme inhibitors. They act by inhibiting entry of influenza virus into uninfected cells and preventing the release of recently formed virus particles from infected cells. Tamiflu is given orally (capsules and solution) and Relenza is given by inhalation (Diskhaler system).

Both have substantial experience of use and favourable benefit-risk profiles.

Tamiflu

Side effect profile

The most common side effects of Tamiflu are nausea, vomiting, diarrhoea, abdominal pain, and headache. These may usually occur after the first dose and will usually stop as treatment continues. The frequency of these effects is reduced if Tamiflu is taken with food. More-serious side effects are very rare (see Summary of Product Characteristics for further information).

The product information for Tamiflu lists neuropsychiatric disorders (reports of convulsions and delirium) in the side-effects section. These events were added to the product information as a precautionary measure—a causal association between Tamiflu and the reported events is uncertain.

Drug interactions

Clinically important drug interactions with Tamiflu are unlikely, including those involving competition for renal tubular secretion. However, care should be taken when prescribing Tamiflu for patients who are taking co-excreted medicines with a narrow therapeutic margin (eg, chlorpropamide or methotrexate).

No dose adjustment is required when coadministering with probenecid in patients with normal renal function. Coadministration of probenecid, a potent inhibitor of the anionic pathway of renal tubular secretion, results in an approximate two-fold increase in exposure to the active metabolite of oseltamivir.

Renal impairment

Dose adjustment is recommended for adults with severe renal insufficiency (ie, ≤30 mL/min). Tamiflu is not recommended for patients with a creatinine clearance of ≤10 mL/min or in those undergoing dialysis.

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National Pandemic Flu Service:
https://www.pandemicflu.direct.gov.uk/

The National Pandemic Flu Service is directing anyone with a kidney disorder to their healthcare professional; Relenza has been procured for these individuals (see below).

Shelf-life

See
http://www.emea.europa.eu/humandocs/PDFs/EPAR/tamiflu/28497109en.pdf

Packs of Tamiflu capsules manufactured since June 2009 have a shelf-life of 7 years. Packs manufactured before then, including most in UK stockpiles, have a shelf-life of 5 years. Although the longer shelf-life cannot be retrospectively applied to the licence for the older packs, the European Medicines Agency (EMEA) has issued guidance that Tamiflu capsules already on the market may be used for up to 2 more years after their current 5-year expiry date during the swine flu pandemic.

See
www.emc.medicines.org.uk

Relenza

Relenza is delivered by inhalation using a Diskhaler. The recommended doses are provided in the product information.

The National Pandemic Flu Service is directing anyone with a kidney disorder or who may be pregnant to their healthcare professional; Relenza has been procured for these individuals.

Side effects

Recognised side effects to Relenza are very rare, but may include allergic-type reactions such as swelling of the face, mouth, or throat; skin rash; or hives. Acute bronchospasm or serious decline in respiratory function (or both) have been seen in patients with a history of asthma or chronic obstructive pulmonary disease (COPD), and in those without a history of respiratory disease (see below).

The product information for Relenza also lists neuropsychiatric disorders as a possible side effect of the medicine. As with Tamiflu, these events were added to the product information as a precautionary measure and a causal association with Relenza is uncertain.

Drug interactions

Clinically significant drug interactions with Relenza are unlikely.

Patients with asthma or COPD

Patients with severe asthma should not receive Relenza unless close medical monitoring and appropriate clinical facilities are available, in case of bronchoconstriction. In patients with persistent asthma or severe COPD, management of the underlying disease should be optimised during Relenza treatment.

If Relenza is considered appropriate for any patient with asthma or COPD, the patient should be informed of the potential risk of bronchospasm and should have a fast-acting bronchodilator available. Patients on maintenance inhaled bronchodilating therapy should be advised to use their bronchodilators before taking Relenza.

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How to report suspected adverse reactions to Tamiflu and Relenza

We have a special web-based system for reporting suspected adverse drug reactions (ADRs) to Tamiflu and Relenza, called the **Swine Flu ADR Portal**. This is available now and will continue to operate for the duration of the pandemic:

- Please report all suspected ADRs to Tamiflu and Relenza via the Swine Flu ADR Portal at www.mhra.gov.uk/swineflu
- Please remember to include the following important information in your report:
  - patient age
  - indication (prophylaxis or treatment)
  - outcome of the ADR
  - information on any underlying risk factors for the ADR or for influenza complications; or state if there are no known risk factors
  - any other information about the patient or additional clinical details that will help us in our assessment of the case
- When swine influenza A/H1N1 vaccines become available, the Swine Flu ADR Portal should also be used to report suspected ADRs to these vaccines
- The existing Yellow Card Scheme will remain in operation during this time for reporting suspected ADRs to all other medicines

Before this swine flu outbreak, use of these medicines in the UK was limited—UK public health policy for prevention of seasonal influenza infection focused on yearly seasonal influenza vaccination. It is possible that the wider prescribing of these medicines in a pandemic situation may reveal rare effects that have not previously been seen. Therefore, it is vitally important that suspected ADRs to Tamiflu and Relenza are reported to us. If you suspect that a patient has experienced an adverse reaction to these antivirals, please report as outlined above.

Given the novel mechanisms that will be in place for provision of antivirals during the pandemic, we particularly welcome reports from patients of suspected side effects to their antiviral medication. Please remind patients that they can report such suspected side effects through the Swine Flu ADR Portal at www.mhra.gov.uk/swineflu

For further information on ADR reporting for Tamiflu and Relenza see letter to healthcare professionals sent July 6, 2009 at http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON051790

Mechanisms in place for diagnosis of swine flu and supply of antivirals

As the swine flu pandemic progresses in the UK, special mechanisms are being put in place by the NHS to ensure that patients are quickly diagnosed with flu and can rapidly access antiviral medication. In England, the National Pandemic Flu Service is now operating. Mechanisms for supply of antivirals may vary between regions depending on local circumstances. Please keep up to date on such mechanisms via the information links, left.

Further information

Northern Ireland

nidirect:
www.nidirect.gov.uk/index/health-and-well-being/swine-flu.htm

Scotland

NHS24:
www.nhs24.com/content/default.asp?page=home_SwineFlu

Wales

National Public Health Service for Wales:
http://www.wales.nhs.uk/sites3/news.cfm?orgid=719&contentid=12625

England

NHS Direct:
http://www.nhs.uk/AlertsEmergencies/Pages/Pandemicflualert.aspx

NHS Choices:
http://www.nhs.uk/Conditions/Pandemic-flu/Pages/QA.aspx

National Pandemic Flu Service:
https://www.pandemicflu.direct.gov.uk/

Hot topic

Herbal products: safety update

Healthcare professionals will often encounter patients who are taking herbal medicines. However, many patients are reluctant to inform their healthcare professional, so enquiry is important. Research commissioned by the MHRA indicated that approximately a third of UK adults had used herbal medicines. These products have the potential to cause adverse reactions as well as interact with conventional medicines.

We are responsible for monitoring the safety of herbal medicines in the UK and to do this we use many of the same tools that are used to monitor conventional medicines. Furthermore, the Herbal Medicines Advisory Committee advises the MHRA on the safety and quality of herbal medicinal products for human use.

Information about herbal medicines is available on our website (see link, left).

Key areas of concern about herbal medicines include:

- Poor and variable quality of unlicensed or unregulated products
- Deliberate adulteration with potentially toxic ingredients such as heavy metals, arsenic, and prescription-only medicines (including products that have been banned because of safety concerns)
- Lack of detailed product information

See Drug Safety Update March 2009, p 11;
www.mhra.gov.uk/mhra/drugsafetyupdate

Further information on the Herbal Medicines Advisory Committee is available at http://www.mhra.gov.uk/Committees/Medicinesadvisorybodies/HerbalMedicinesAdvisoryCommittee/index.htm

See http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Adviceandinformationforconsumers/Usingherbalmedicines/index.htm

For the latest herbal safety news, see http://www.mhra.gov.uk/Howweregulate/Medicines/Herbalandhomoeopathicmedicines/Herbalmedicines/HerbalSafetyNews/Currentsafetyissues/index.htm

After international case reports of liver damage, we have recently issued warnings in conjunction with the Food Standards Agency about Hydroxycut (a weight-loss supplement) and Fortodol (also sold as Miradin, a turmeric-based food supplement, often promoted with unsubstantiated medicinal claims).

Regulated herbal medicines

There is an increasing range of herbal medicines with a traditional herbal registration (shown by a THR number on the packaging) coming onto the UK market. We have assessed safety, quality, and patient information for these products. The permitted minor indications are based on evidence of traditional use and not proven efficacy. There are also some herbal medicines with a product licence (shown by a PL number) which are accompanied by necessary information for safe use.

From MHRA homepage www.mhra.gov.uk use the A–Z index to find Public Assessment Reports for herbal medicines, which contain details of product information

Details of the Summary of Product Characteristics and patient leaflets for products registered under the THR scheme are available on our website.

The Yellow Card Scheme

The Yellow Card Scheme (www.yellowcard.gov.uk) collects reports of suspected adverse reactions and is a valuable tool when trying to identify new safety issues for medicinal products, including herbals. The number of reports received of adverse reactions that are suspected to be associated with herbal products is very low (see table below), and we would like to encourage everyone to report all adverse reactions suspected to be due to herbal products. Increasing the number of good-quality reports increases the chance of detecting potential side effects and assists assessment of the risk.

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The table shows the number of reports of suspected adverse reactions to a herbal product received through the Yellow Card Scheme:

Year	Number of reports
2006	109
2007	77
2008	98
2009*	43

*To May 31, 2009.

It is not clear why the level of reporting is so low for herbal products. However, possible reasons include:

- Lack of discussion between patients and healthcare professionals about the use of herbal medicines
- Doubt about whether the product is a herbal medicine, a homoeopathic product, or even a food supplement
- Doubt regarding the regulatory status of products and what can be reported
- Tendency to believe that natural means safe

The Yellow Card Scheme accepts reports of adverse reactions to all products. If you **suspect it: report it**, irrespective of a product's status or classification.

Concern	Action
Licensed **or** unlicensed product	**Report it**—giving as much detail as possible about the product
Herbal medicine **or** food supplement	**Report it**—giving as much detail as possible about the product
Not sure what caused the reaction	**Report it**—include details of all medicinal and herbal products taken by the patient

Yellow Card reporting requirements

See Drug Safety Update February 2009, p 5 for further guidance on completing a Yellow Card; see also www.yellowcard.gov.uk

When submitting a Yellow Card for a herbal product, please use the same reporting forms and procedures as for medicines. However, we would appreciate it if you could provide some extra details, particularly as much information as possible about the herbal product suspected to be involved, such as:

- The brand name (if it has one)
- The list of ingredients
- Ideally, a copy of package labelling
- Details of the manufacturer

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We ask for these details because there are numerous products that are sold using the botanical name such as "Echinacea"; however these products can differ depending on the formulation or the species involved, and may be associated with different side-effect profiles. Without the additional details it is difficult for us to identify new safety issues with particular herbal products.

For serious adverse reactions, it is worth considering asking the patient to retain the herbal product in case we wish to test the product. We may test it if it is suspected that the product may contain an illegal ingredient such as a banned or restricted herb, or a prescription-only medicine. Illegal ingredients are commonly found in products used for slimming or erectile dysfunction.

If you report a suspected adverse reaction to a herbal product on behalf of a patient, please keep a note of the patient's contact details in case further information is needed.

We encourage everyone to report without delay any case of an adverse reaction suspected to have been caused by a herbal product or products.

Hot topic

Monitoring the impact of regulatory action taken by the MHRA

The MHRA is very aware of the need to monitor the impact of the actions we take on medicines, whether these result in a widening or restriction of access. It is important for us to ensure that our decisions have a positive outcome for users of medicines.

Our commitment to this important area of research is outlined in our current business plan. This article outlines how we try to ensure we optimally safeguard public health by: conducting our own research; working collaboratively with academic groups and other agencies; commissioning research; and requesting specific research from the pharmaceutical industry (marketing authorisation holders) where appropriate.

Access our 2009/10 business plan at http://www.mhra.gov.uk/home/groups/es-policy/documents/publication/con043990.pdf

MHRA research

We perform studies to provide better information on the pattern of usage of medicines to inform decisions we are about to make; or to examine the impact of regulatory action that has been taken. For example, we might need to identify patterns of use for established medicines before reclassification of a product from prescription-only to pharmacy supply; to examine patterns of use after regulatory action; or assess usage of other medicines in the event of a drug withdrawal.

We also carry out studies to investigate potential new safety issues using databases such as the General Practice Research Database.

See www.gprd.com

Commissioned research programme

See www.mhra.gov.uk/NewsCentre/CON2030212

In April 2005, we announced a call for research proposals to study the safety of medicines. As a result, the following studies were commissioned:

- The safety of antiepileptic drugs in children (London School of Pharmacy)

This study specifically looked at the safety of newer antiepileptics compared with the more-established drugs in children, and did not identify any specific safety concerns. This study was presented at the European Society for Developmental Perinatal and Paediatric Pharmacology, Rotterdam 2008, and the International Conference of Pharmacoepidemiology, Copenhagen 2008.

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- The impact of regulatory action taken by the MHRA on COX-2 inhibitors[1] and SSRIs[2,3] (University of Bristol)

The COX-2 study aimed to investigate the effects of withdrawal and regulatory advice for COX-2 inhibitors on UK rates of gastrointestinal haemorrhage and acute myocardial infarction. It found that such action did not appear to have any adverse effect on population health and may have been beneficial.

The SSRI studies analysed whether the restriction of the use of SSRIs in children and adolescents had lead to an increased risk of suicide in these age-groups, and found that there was no evidence that this had occurred.

- The use of the General Practice Research Database to provide earlier information on the safety of drug use in children before conducting a trial (Queen Mary and Westfields College London, study ongoing)

It is hoped that a preliminary study using this database could help researchers plan their trial specifically for the target population.

Collaborative work

We also work collaboratively with external academic groups or other government agencies (such as the Health Protection Agency) to carry out studies of mutual interest. Examples of such collaborations include:

- University of Bristol—risk of suicidal behaviour related to antidepressants[4] and smoking-cessation therapies (submitted for publication)

This antidepressant study[4] found no evidence that the risk of suicide or non-fatal self-harm in adults prescribed SSRIs was greater than in those prescribed tricyclic antidepressants. Weak evidence was found for an increased risk for current SSRI use in those age 18 years or younger. However, a bias of preferential SSRI prescribing to patients at higher risk of suicidal behaviour cannot be ruled out.

- Health Protection Agency—risks of Guillain-Barré syndrome and Bell's palsy after influenza vaccination[5,6]

These studies found no evidence of increased risk.

- University of Oxford, Cancer Research UK Epidemiology Unit—GP prescribing trends in HRT, tibolone, and bisphosphonates between 1991 and 2005 for prevention and treatment of osteoporosis in relation to published research on health effects of these medicines and changes to prescribing advice[7]

The study found that prescribing of HRT had fallen by about 50% since 2002, which reflected new epidemiological evidence and prescribing advice. Bisphosphonate prescribing increased during the study period, partly reflecting the availability of weekly formulations.

External research groups

In addition to specific collaborative studies, the MHRA has good links with various academic research groups and monitors the published literature, for research relevant to regulatory action that we may have taken. One example of this is the recent work published by K Hawton and colleagues[8] on the effect of the phased withdrawal of coproxamol on deaths from drug poisoning.

Research by the pharmaceutical industry

A marketing authorisation holder for a medicine is required to agree at the time of \licensing what research they intend to conduct to gather further information on the safety of their products. Although post-authorisation studies have been conducted for

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1 Wheeler B, et al. *Br J Clin Pharmacol* accepted article July 6 2009; doi 10.1111/1365-2125.2009.03500.x. See http://www3.interscience.wiley.com/journal/122518707/abstract (accessed July 22, 2009).

2 Wheeler B, et al. *Pharmacoepidemiol Drug Saf* 2009; **18:** 579–88.

3 Wheeler B, et al. *BMJ* 2008; **336:** 542–45.

Health Protection Agency: www.hpa.org.uk

4 Martinez C, et al. *BMJ* 2005; **330:** 373–74.

5 Stowe J, et al. *Am J Epidemiol* 2009; **169:** 382–88.

6 Stowe J, et al. *Hum Vaccin* 2006; **2:** 110–12.

7 Watson J, et al. *Eur J Clin Pharmacol* 2007; **63:** 843–49.

8 Hawton K et al. *BMJ* 2009; **338:** b2270.

For an example summary of a risk management plan for the smoking-cessation treatment varenicline, see http://www.emea.europa.eu/pdfs/human/euleg/9626805en.pdf p40.

For further information on risk management plans see http://www.emea.europa.eu/pdfs/human/euleg/9626805en.pdf

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many years,[9] the legal requirement for risk management plans is more recent.

A risk management plan provides an overview of the known safety profile of the product by summarising the data from clinical trials and other studies. Any important identified risks are also discussed, along with the proposals for minimising these risks and for further studies to investigate the safety of the product once it is in routine use. Generally, marketing authorisation holders are responsible for carrying out these studies, but the methodology is discussed and agreed with the regulatory authority.

9 Waller P, et al. *BMJ* 1992; **304:** 1470–72.

Stop press

Rotigotine patches: lifting of prescribing restrictions

In July 2008, restrictions were placed on prescribing of the **rotigotine transdermal patch** (Neupro▼). These restrictions limited prescribing to 1 month's supply and also asked that no new patients were initiated.

These restrictions arose because of reports of the development of crystals in some patches due to storage conditions. A cold-chain storage and distribution system has now been fully implemented by the manufacturer—all stocks of rotigotine patches are refrigerated from manufacturer to patient. No significant crystallisation should occur under these storage conditions. As a result, the restrictions on prescribing have now been lifted.

Advice for healthcare professionals:

- Rotigotine patches can once again be prescribed in line with the approved indications of idiopathic Parkinson's disease or restless legs syndrome
- Prescriptions are no longer limited to 1 month's supply
- Patient should store their patches in the refrigerator; patches must not be stored in the freezer. There is no need to bring the patch to room temperature before application

See information from the European Medicines Agency http://www.emea.europa.eu/humandocs/PDFs/EPAR/neupro/32296409en.pdf and a letter sent to healthcare professionals in June 2009 at http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/index.htm

'First Steps' infant medicine feeder: recall due to overdose risk

The MHRA is supporting the recall of the 'First Steps' infant medicine feeder (item number FS012), the use of which has led to a serious paracetamol overdose in a 6-month-old infant. The medicine feeder has two scales, millilitres (mL) and teaspoons (tsp). Confusion between the scales led to the 6-month-old infant being repeatedly administered 2·5 tsp (about 13 mL) of paracetamol instead of 2·5 mL.

The manufacturer, RSW International Ltd, issued a recall notice to their customers (both retail and wholesale) on June 12, 2009. However, this notice may not have reached all retail outlets or parents and carers who have already purchased a medicine feeder. We have issued a medical device alert to the health service. Very large numbers of this product have been on sale, and we are asking for your help in bringing this recall to the attention of any parents and carers who may have purchased the product. Where possible, please consider displaying our press release on this issue (see link, left) in public areas where parents and carers of babies and young infants may see it.

Anyone who has purchased this infant medicine feeder should stop using the product and dispose of it.

See our News Centre http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON049200 and medical device alert: http://www.mhra.gov.uk/Publications/Safetywarnings/MedicalDeviceAlerts/CON051931

Other information from the MHRA

Patient Information Leaflet of the month: Symbicort

Access PIL of the month at http://www.mhra.gov.uk/Howweregulate/Medicines/Labelspatientinformationleaflets andpackaging/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 with 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 initiative, we are publishing a series of examples of best practice on our website. The latest in the series is for **Symbicort**, which contains **budesonide and formoterol** and is indicated for the management of asthma and in chronic obstructive pulmonary disease. The leaflet shows how colour can be used to highlight the information pertinent to different patient groups, which in testing was found to be helpful.

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

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