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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We would like to remind prescribers that tacrolimus products—Advagraf, Prograf, and the newly launched Modigraf ▼—are not interchangeable without careful therapeutic monitoring. Our article on p 2 brings you information on the new oral liquid formulation of tacrolimus (Modigraf), which is suitable for paediatric use.

This month we also bring you an update on reports of suspected adverse reactions we have received for flu antivirals and vaccines (p 3). To date, the balance of risks and benefits for these medicines and vaccines remains positive and no new safety issues have been identified. Further information is available at www.mhra.gov.uk/swineflu.

Finally this month, news on obesity medicines: we have a safety update on orlistat—particularly the Pharmacy formulation (alli, p 4). We are also aware that consumers may be at risk after reports in the USA of counterfeit alli that contained sibutramine rather than orlistat. Moreover, a Europe-wide review has led to the recommendation to suspend the licences for sibutramine across the EU because of new evidence indicating risks outweigh benefits (p 7).

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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.

Tacrolimus: new oral liquid (Modigraf ▼); formulations not interchangeable without careful therapeutic monitoring

Keywords: tacrolimus, Modigraf ▼, Prograf, Advagraf

Tacrolimus is now available in granules as Modigraf ▼, which can be used to prepare an immediate-release oral liquid. This preparation has approximately 18% increased bioavailability when compared to Prograf capsules. It is important to note the correct use of tacrolimus products as outlined below. Oral tacrolimus formulations or regimens should not be altered without careful therapeutic monitoring by a transplant specialist

Tacrolimus is an immunosuppressant used to prevent organ transplant rejection. In addition to Prograf capsules, the existing orally administered immediate-release formulation, tacrolimus is now available in granules, which can be used to prepare an oral liquid (Modigraf ▼), also for twice-daily dosage. Modigraf can be used in paediatric patients because it is suitable for those who are unable to swallow capsules, and it allows flexible dosing based on bodyweight.

Care when prescribing and dispensing tacrolimus products

Tacrolimus is also available as prolonged-release capsules, Advagraf, which must be taken once a day in the morning. We have previously published advice on the care needed when prescribing and dispensing the correct tacrolimus product after reports of medication errors that have resulted from unintended switching between Prograf and Advagraf.

See Drug Safety Update January 2009, p 4; www.mhra.gov.uk/drugsafetyupdate

Prescribers and pharmacists need to be fully aware of the addition of Modigraf ▼ to the oral tacrolimus product range. Modigraf is indicated for the prophylaxis of transplant rejection in adult and paediatric recipients of a kidney, liver, or heart transplant. It is also indicated for treatment of allograft rejection resistant to treatment with other immunosuppressive medicines in adults and children. The preparation has approximately 18% increased bioavailability when compared to Prograf capsules.

Need for clinical monitoring with treatment changes

Information on converting patients between Prograf and Modigraf ▼ is given in the product information. Switching between Advagraf and Modigraf ▼ is not recommended. Oral tacrolimus formulations or regimens should not be altered without careful therapeutic monitoring by a transplant specialist.

Product information is available on the European Medicine Agency's website at http://www.ema.europa.eu/humandocs/PDFs/EPAR/modigraf/emea-combined-h954en.pdf and at http://emc.medicines.org.uk/

Advice for healthcare professionals:

- Prescribers and dispensers should take note of the different bioavailabilities of the available oral formulations of tacrolimus
- Monitor patients carefully when switching between formulations of tacrolimus, or from unlicensed medicines to Modigraf ▼ (see below)
- Take care in prescribing or dispensing the correct product/formulation of tacrolimus

Use of unlicensed tacrolimus formulations

Patients unable to swallow Prograf capsules may have previously been given the contents of the capsules in water before swallowing or may have used extemporaneously prepared or unlicensed liquid preparations ('specials'). The

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bioavailability of such manipulations or preparations is unknown and may vary between manufacturers or from batch to batch. Special care must be taken when converting patients from unlicensed 'special' oral liquid preparations to licensed formulations of tacrolimus. The transfer of patients from any unlicensed treatment to Modigraf ▼ should be closely supervised by a transplant specialist.

For information on prescribers' responsibilities see Drug Safety Update April 2009, p 6; www.mhra.gov.uk/drugsafetyupdate

Before using an unlicensed medicine or a licensed medicine off-label, prescribers should satisfy themselves that an alternative, licensed medicine such as Modigraf ▼ would not meet the patient's needs.

Advice for healthcare professionals:

- Consider use of the licensed oral liquid formulation of tacrolimus (Modigraf ▼) for paediatric patients and others with swallowing difficulties
- Please report any suspected adverse reactions to tacrolimus products (recording the product/formulation used) on a Yellow Card (see www.yellowcard.gov.uk)

Yellow Card Scheme update

Problem with postal delivery of Yellow Cards

We have identified a problem with the Yellow Card postal delivery service. Some Yellow Cards have been returned to sender due to an error in the Royal Mail. If you have posted a Yellow Card report form to us and have either had it returned or not received an acknowledgement letter we kindly ask you to resend the report. This can be done by sending a new report form or reporting online at www.yellowcard.gov.uk

The issue with Royal Mail has now been rectified and online reporting is unaffected.

We apologise for the inconvenience and appreciate your effort in reporting to the Yellow Card Scheme.

Swine flu portal update

Suspected adverse reactions to flu antivirals and vaccines confirm recognised safety profile

This article updates you on reports of suspected adverse reactions received up to Jan 19, 2010 for the antiviral medicines and vaccines in use to help manage swine flu.

You can still report suspected adverse reactions to these medicines and vaccines at www.mhra.gov.uk/swineflu, where further information is also available.

Pandemic vaccines

Celvapan and Pandemrix are the swine flu H1N1 vaccines in use in the UK. As of Jan 17, 2010, more than 4 million doses of these vaccines (mostly Pandemrix) have been given in the UK, including at least 132 000 in pregnant women. Up to and including Jan 19, 2010, we have received a total of 2817 UK reports of suspected ADRs to the H1N1 vaccines. The 2817 reports include a total of 7487 suspected reactions.

No unexpected new safety issues have been identified from reports received to date. The balance of benefits and risks for Celvapan and Pandemrix remains positive. Most reports received are for Pandemrix (87%, n=2451), which is likely to

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be due to higher use of this vaccine in the UK.

The total number and the nature of suspected adverse effects reported are very much as we expected at this stage in the immunisation campaign. The most frequently reported suspected adverse effects are injection site reactions (eg, pain, swelling, redness), or are well established adverse effects of many vaccines, including the swine flu vaccines (eg, nausea, vomiting, dizziness, muscle pain, fever, fatigue, headache, swollen glands, flu-like illness). In general, these are neither serious nor long-lasting. For the isolated cases of other medical conditions reported, the available evidence does not suggest that the vaccine caused the condition and these may have been coincidental events.

Seven cases of suspected Guillain Barre syndrome (GBS) have been reported in the UK up to Jan 12, 2010. There is currently no evidence across Europe that H1N1 vaccines cause GBS or other similar neurological conditions and these were most likely to be coincidental events.

18 deaths, including three cases of intrauterine death, following Pandemrix have been reported in the UK up to Jan 19, 2010. There is currently no suggestion that the vaccine contributed to any of these deaths. Following analyses of the expected numbers of (background) adverse events in pregnancy relative to the number of pregnant women immunised, there remains no evidence of any risks to pregnancy due to the vaccine.

Oseltamivir and zanamivir

Up to and including Jan 19, 2010, MHRA has received a total of 1061 reports (including 1908 suspected adverse reactions) for oseltamivir and 34 reports (including 62 suspected adverse reactions) for zanamivir.

There have been at least 1 125 627 treatment courses of oseltamivir and 14 558 treatment courses of zanamivir between July 23, 2009 and Jan 12, 2010.

The balance of risks and benefits for oseltamivir and zanamivir within their licensed indications remains positive, and no new safety issues have been identified. There remains no evidence to suggest that they carry any risks to pregnancy. The most common suspected reactions are consistent with the signs and symptoms of flu-like illness, or are recognised side effects of these medicines

The safety of these vaccines and antivirals will continue to be kept under close review. You can help us by reporting any suspected adverse reactions via www.mhra.gov.uk/swineflu

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Hot topic

Orlistat safety update

Orlistat is a potent, specific, and long-acting inhibitor of gastrointestinal lipases. It exerts its therapeutic activity in the lumen of the stomach and small intestine by preventing the gastric and pancreatic lipases from hydrolysing dietary fat, in the form of triglycerides, into absorbable free fatty acids and monoglycerides.

Orlistat is available in Europe as 120 mg capsules under the brand name Xenical, and as 60 mg capsules under the brand name alli, for weight loss in combination with a reduced-calorie, lower-fat diet. Xenical has been licensed since 1998 and is available as a prescription-only medicine; alli was licensed in January 2009 and is available without a prescription under the supervision of a pharmacist.

See also Drug Safety Update May 2009, p 6;
www.mhra.gov.uk.mhra/drugsafetyupdate

alli: updated safety information

A recent Europe-wide review of the safety information for alli has led to a number of updates, which bring the product information in line with that for Xenical. Pharmacists

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Hot topic *Cont.*

Further information is available in a letter for pharmacists, sent Nov 30 2009, available at http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON063058

For further information on the counterfeit reports see our News Centre: http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON068520; suspected counterfeit medication can be reported in confidence at counterfeit@mhra.gsi.gov.uk or on 020 7084 2701. See also p 7 for information about the recommendation to suspend the EU licences for sibutramine due to negative balance of benefits and risks.

should be aware of this information so that they can appropriately advise consumers who wish to buy alli or discuss its use.

Oxalate nephropathy

Patients with kidney disease should consult a doctor before starting alli because use of orlistat could rarely (≥1/10 000 to <1/1000) lead to hyperoxaluria and oxalate nephropathy.

Interaction with levothyroxine

Patients who are taking levothyroxine should consult a doctor before starting alli because reduced control of hypothyroidism may occur when alli and levothyroxine are taken at the same time. This could be due to decreased absorption of iodine salts or levothyroxine (or both). These medicines may need to be taken at different times to reduce the risk of interaction, and the dose of levothyroxine may need to be adjusted.

Interaction with antiepileptic drugs

Patients who are taking an antiepileptic drug should consult a doctor before starting alli because loss or seizure control have been reported during concomitant treatment with orlistat and antiepileptic drugs such as sodium valproate and lamotrigine. Orlistat may decrease the absorption of antiepileptic drugs, leading to loss of seizure control. During concomitant treatment, patients should be monitored for possible changes in the frequency and severity of convulsions. If this occurs, consideration could be given to administering orlistat and antiepileptic drugs at different times.

Pancreatitis

Pancreatitis has also been added as an undesirable effect of alli treatment after reports in a number of patients (frequency unknown).

alli: reports of counterfeit capsules in the USA

We are aware that consumers may be at risk after reports in the USA of counterfeit alli that contained sibutramine rather than orlistat. Although the counterfeit product has not been found in the UK, it is still potentially available to UK customers via the internet. Consumers should not buy medicines from unregulated websites.

Review of hepatotoxicity with orlistat

In July 2009, there was a Europe-wide review of a possible association between orlistat and serious hepatic reactions. The review included non-clinical, clinical trial, and post-marketing safety data provided by the licence holders and a review of suspected adverse reaction reports submitted to the MHRA. Data from the licence holders have also been submitted to the US Food and Drug Administration, which is also conducting a review.

The European review concluded that there is insufficient evidence to show that Xenical or alli are associated with more serious liver disorders than those already listed in the product information, and that no further action was recommended at this time.

The current product information for Xenical and alli contains a warning that hepatitis, cholelithiasis, and increased transaminases and alkaline phosphatase are possible side effects, and that patients who experience symptoms such as yellowing of the skin and eyes, itching, stomach pain, and liver tenderness should stop taking the capsules and tell their doctor.

The MHRA, together with European regulatory authorities, will continue to monitor all adverse reactions associated with orlistat. Suspected adverse reactions can be reported to us via the Yellow Card Scheme (see www.yellowcard.gov.uk) and we welcome reports direct from patients.

Hot topic

- There is a new element to the indication for nicotine replacement therapy (NRT) of "harm reduction", since it has become widely accepted that there are no circumstances in which it is safer to smoke than to use NRT
- The extension of the indication for NRT to include harm reduction raises the question of the regulation of other unlicensed nicotine containing products on the market such as electronic cigarettes, which have not been assessed for safety, quality, and efficacy
- The MHRA has launched a public consultation on whether/how to bring these products into regulation. All comments are welcome and should be submitted to Amanda Bryan (Amanda.bryan@mhra.gsi.gov.uk) by 4 May 2010

Nicotine replacement therapy and harm reduction

Reducing the adverse impact of smoking on health remains a high priority for government, and over several years the MHRA has been in discussion with the Department of Health and other interested parties to determine and implement actions necessary for the effective regulation of nicotine delivery products. This evolving approach has focussed on extending access to new patient populations and supporting wider access to new formulations of nicotine replacement therapy (NRT).

An Expert Working Group set up in 2005 reviewed the usage of NRT and recommended that restrictions on use for all NRT products should be minimised for pregnant and breastfeeding women; patients with heart disease; patients with kidney or liver problems; patients with diabetes; and children aged 12–18 years. Since then the indication for NRT has been extended, such as by 'cut down to quit' and 'temporary abstinence' introduced in 2005 and 2006, supported by data from clinical trials showing NRT as an effective intervention in achieving sustained smoking abstinence for smokers who have no intention to stop completely, or who are unable to attempt an abrupt quit.

Since the advice of the Working Group in 2005, it has become widely accepted that there are no circumstances in which it is safer to smoke than to use NRT, and following advice from the Commission on Human Medicines (CHM) in October 2009, the MHRA has approved an extension to the indication to include a 'harm reduction' element for a particular product—the Nicorette Inhalator either as a complete or partial substitute for smoking. This now includes its use in those who choose or are forced into temporary abstinence (i.e. who do not wish to expose others to their second-hand smoke or cannot smoke because they are in a smoke-free area), and those who wish to reduce the number of cigarettes smoked without a specific intention to quit completely, without a limit to the duration of use.

The CHM also agreed the principle for all currently licensed forms of NRT and advised that there should be an indication for the harm reduction approach in pregnancy. It is important to be clear that smokers should quit without the use of NRT if they are able to, particularly in pregnancy and in patients with very severe pre-existing cardiovascular disease; however, it is also recognised that the use of NRT could increase, by several fold, the chances of a successful quit attempt and that there are consequences of failed quit attempts, including lifelong effects on the unborn child.

The products with the new indication are expected to be on the market in 2010. The 'harm reduction' approach to the use of NRT is a significant plank of the wider tobacco strategy launched on 1 February 2010 (www.dh.gov.uk).

The extension of the indication for NRT to harm reduction marks a major shift in approach in medicines regulation. NRT has to date not been licensed for harm reduction and the decision to do so raises the question of the regulation of other unlicensed nicotine containing products on the market such as electronic cigarettes, which have not been assessed for safety, quality, and efficacy. The MHRA has launched a public consultation exercise on whether/how to bring these products into regulation (www.mhra.gov.uk). All comments are welcome and should be submitted to Amanda Bryan (Amanda.bryan@mhra.gsi.gov.uk) by 4 May 2010.

Stop press

Sibutramine: suspension of EU licences recommended as evidence indicates risks outweigh benefits

The European Medicines Agency (EMA) has completed a review of the obesity medicine sibutramine (Reductil) on the basis of new safety information from a large clinical trial, the Sibutramine Cardiovascular OUTcomes (SCOUT) study. The review has found that the cardiovascular risks of sibutramine outweigh its benefits. The EMA's Committee for Medicinal Products for Human Use (CHMP) has recommended suspension of the licences for this medicine across the European Union.

SCOUT was a randomised, double-blind, placebo controlled study in approximately 10 000 obese and overweight patients with cardiovascular disease and/or type 2 diabetes treated over a 6-year period. The results showed that these high-risk patients treated with sibutramine had a 16% increased risk of cardiovascular adverse events such as myocardial infarction and stroke compared with placebo-treated patients (hazard ratio 1·161 [95% CI 1·029–1·311]; p=0·016). Furthermore, the mean weight loss achieved with sibutramine in all clinical trials is modest, decreasing bodyweight by approximately 2–4 kg more than placebo which may not be sustained after cessation of treatment.

Advice for healthcare professionals:

- Doctors should not issue any new prescriptions for sibutramine, and should review the treatment of those who are currently taking this medicine
- Pharmacists should not dispense any prescriptions for sibutramine and should advise patients to make an appointment to see their doctor at the next convenient time
- Patients who are currently being treated with sibutramine should be advised to schedule an appointment with their doctor at the next convenient time to discuss alternative measures to lose weight, including use of diet and exercise regimes. Patients may stop sibutramine treatment before their appointment if they wish

Further information is available at http://www.ema.europa.eu/pdfs/human/referral/sibutramine/3940810en.pdf and http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON068475

Off-label intraocular use of recombinant tissue plasminogen activator: risk of intraocular lens opacification

We have received five reports of opacification of intraocular lenses associated with off-label intraocular injections of recombinant tissue plasminogen activator. In the reported cases, recombinant tissue plasminogen activator has been injected intracamerally for the treatment of uveitis-related fibrosis. Alteplase is a drug indicated for use in acute stroke, myocardial infarction, and pulmonary embolism. It is not licensed for intracameral use. Off-label intravitreal injection may also pose similar risks. The exact mechanism by which recombinant tissue plasminogen activator may cause such opacification is unknown at present. Healthcare professionals should ensure adequate follow-up of patients at risk of this side effect, and all relevant professionals should be aware of this risk.

All cases of intraocular lens opacification should be reported to the MHRA, including those which may be related to the off-label use of medicines. This issue will be kept under review with monitoring for further reports.

See http://www.mhra.gov.uk/Safetyinformation/Reportingsafetyproblems/index.htm and http://www.mhra.gov.uk/Publications/Safetywarnings/MedicalDeviceAlerts/CON068463

Please report suspected adverse reactions associated with intra-articular use of local anaesthetics

See http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm190302.htm

The US Food and Drug Administration has recently reported that it has received 35 reports of chondrolysis involving patients given continuous (48–72 hours) intra-articular infusions of local anaesthetics (with or without epinephrine/adrenaline) to control pain after surgery.

Chondrolysis has been observed mainly in otherwise healthy young adults after surgery to the shoulder joint. In more than half of these reports, the patients required additional surgery, including arthroscopy or arthroplasty.

Single intra-articular injections of local anaesthetics in orthopaedic procedures have been used for many years without any reported occurrence of chondrolysis. To date, we have received no reports of chondrolysis in association with intra-articular administration of local anaesthetics from UK sources. Please report via the Yellow Card Scheme any cases of suspected adverse drug reactions associated with intra-articular administration of local anaesthetics.

See www.yellowcard.gov.uk

Other information from the MHRA

Patient Information Leaflet of the month: amoxicillin

Access PIL of the month 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 them 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 new initiative, we are publishing a series of examples of best practice on our website. The latest in the series is for **amoxicillin**, which is used in the treatment of infections. The leaflet design uses good navigation tools and in testing was found to be well received by patients.

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

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