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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Medicines that are used to treat various infections form the theme of our articles in *Drug Safety Update* this month.

Ketoconazole, an antifungal agent, has recently had a review of its risks and benefits. Because of the risk of serious hepatotoxicity, ketoconazole should be used only for dermatophytosis, *Malassezia* folliculitis, and chronic candidosis that cannot be treated topically (p 2).

Tazocin, which contains the active ingredients piperacillin and tazobactam, has been reformulated, improving its physical compatibility. Tazocin is now compatible with lactated Ringer's (Hartmann's) solution and, in some circumstances, aminoglycosides (p 3). Look out for a new package colour marked "new formulation".

Telbivudine is a new nucleoside analogue for adults with chronic hepatitis B. Our advice to healthcare professionals is that the combination of telbivudine and interferon cannot be recommended because of a risk of peripheral neuropathy. Find out more on page 4.

Claire Tilstone, Editor
drugsafetyupdate@mhra.gsi.gov.uk

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

Ketoconazole: restricted indications

Keywords: ketoconazole, Nizoral, antifungal, hepatotoxicity, restricted indications

Because of the risk of serious hepatotoxicity, oral ketoconazole should be used only for dermatophytosis, *Malassezia* folliculitis, and chronic candidosis that cannot be treated topically

Ketoconazole (Nizoral) is an imidazole antifungal agent, with a spectrum of activity against dermatophytes, yeasts, and other pathogenic fungi. After a review of the risks and benefits, prescribing advice for ketoconazole tablets has been updated.

Several therapeutic indications have been removed because of the risk of serious hepatotoxicity with oral ketoconazole (including cases which had a fatal outcome or required liver transplantation) and because of the availability of other effective antifungal treatments. The approved therapeutic indications are now restricted to:

- Treatment of dermatophytosis and *Malassezia* (previously called *Pityrosporum*)) folliculitis that cannot be treated topically because of the site, extent of the lesion, or deep infection of the skin resistant to, or in patients intolerant of, fluconazole, terbinafine, and itraconazole
- Treatment of chronic mucocutaneous candidosis, cutaneous candidosis, and oropharyngeal candidosis that cannot be treated topically because of the site, extent of the lesion, or deep infection of the skin resistant to, or in patients intolerant of, both fluconazole and itraconazole

The risk of serious hepatotoxicity with oral ketoconazole increases with duration of treatment. Courses of longer than 10 days should be given only after full consideration of the extent of treatment response and of the balance of risks and benefits of continuing treatment.

Liver function must be monitored in all patients who are receiving ketoconazole tablets. Tests should be done before starting treatment, at week 2 and week 4 of treatment, and then continued monthly. Treatment should be stopped if any liver parameters are elevated above three times the normal limit.

Advice for healthcare professionals:

- Ketoconazole tablets are not suitable as a first-line treatment or for superficial infections
- Ketoconazole tablets should be initiated by a physician who is experienced in the management of fungal infections
- Use only when potential benefits are considered to outweigh potential risks, taking into consideration the availability of other effective antifungal therapy
- Risk of serious hepatotoxicity increases with duration of treatment
- Liver function must be monitored before starting treatment, at week 2 and week 4 of treatment, and then monthly

Refer to the full Summary of Product Characteristics for additional information on contraindications, warnings, drug interactions, and adverse events.

For a Dear Healthcare Professional Letter for ketoconazole tablets sent February 2008, see http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/index.htm

Access the Summary of Product Characteristics at http://emc.medicines.org.uk/

Tazocin (piperacillin/tazobactam): new formulation

Keywords: Tazocin, piperacillin/tazobactam, reformulation, compatibility

Tazocin (piperacillin/tazobactam) has been reformulated to meet European Pharmacopoeia requirements on particle size. It contains additional ingredients and is now compatible with a wider range of products

Tazocin (piperacillin/tazobactam) is used to treat a wide range of infections. Because of changes to the European Pharmacopoeia, the medicine has been reformulated and now has two additional excipients: edetate disodium dihydrate (EDTA) and citric acid.

These additional excipients have improved the physical compatibility of the medicine. The new formulation of Tazocin is now compatible with lactated Ringer's (Hartmann's) solution and, in some circumstances, with aminoglycosides. Although generally the mixing of beta-lactam antibiotics with aminoglycosides can inactivate the aminoglycoside, amikacin and gentamicin are compatible with reformulated Tazocin at specific concentrations.

The addition of EDTA to Tazocin has increased the amount of sodium in the product, which equates to a sodium load of 5·58 mEq (128 mg) per 2·25 g dose of Tazocin and 11·16 mEq (256 mg) sodium per 4·5 g dose of Tazocin.

The new formulation is being launched in March 2008. The Marketing Authorisation holder, Wyeth, is taking steps to minimise the amount of time the two formulations are in the supply chain concurrently. Where appropriate, healthcare professionals should use all existing stock before introducing the reformulated product.

The labelling has been revised to help identify the reformulated product. Pack colours have been changed and all packaging components have been clearly marked as "new formulation".

Advice for healthcare professionals:

- Tazocin has been reformulated and is now compatible with a wider range of products
- Sodium load has increased to 5·58 mEq per 2·25 g dose and to 11·16 mEq per 4·5 g dose
- Use-up existing stock before introducing the reformulated product into clinical areas
- Product labelling includes reference to the new formulation to aid identification

The image below shows the new product labelling for reformulated Tazocin:

Telbivudine: risk of peripheral neuropathy with pegylated interferon

Keywords: telbivudine, Sebivo, pegylated interferon, peripheral neuropathy, hepatitis B

Patients who take telbivudine and (pegylated) interferon are at increased risk of peripheral neuropathy. Patients who develop symptoms of peripheral neuropathy should stop taking both medicines

Telbivudine (Sebivo ▼) is a new nucleoside analogue that is indicated for treatment of chronic hepatitis B in adults with compensated liver disease and evidence of viral replication, persistently elevated serum alanine aminotransferase (ALT), and histological evidence of active inflammation or fibrosis (or both).

To read more about the assessment of telbivudine at licensing, access the European Public Assessment Report at http://www.emea.europa.eu/humandocs/Humans/EPAR/sebivo/sebivo.htm

The risk of peripheral neuropathy with telbivudine has been under review since the time of licensing.

Up to the end of January 2008, six cases of peripheral neuropathy have been reported in association with telbivudine monotherapy.

In an ongoing multicentre trial comparing telbivudine monotherapy with telbivudine and pegylated interferon alfa 2a (Pegasys) combination therapy, eight cases of peripheral neuropathy have been reported in 48 patients. The combination arm of this trial was suspended in January 2008. These cases were serious, occurred in relatively young patients within 3 months of starting treatment, and required treatment discontinuation.

See also a letter sent to healthcare professionals in February 2008. http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/index.htm

Advice for healthcare professionals:

- The combination of telbivudine and interferon cannot be recommended
- All patients who take telbivudine should be monitored for occurrence of peripheral neuropathy
- Patients who are taking telbivudine and (pegylated) interferon who develop peripheral neuropathy should stop taking both medicines
- For patients who are taking telbivudine alone who develop peripheral neuropathy, consideration should be given to stopping this medicine

Modafinil: serious skin reactions, hypersensitivity, and psychiatric symptoms

Keywords: Provigil, modafinil, Stevens Johnson Syndrome, erythema multiforme, angioedema, hypersensitivity, suicidality, hallucinations, aggression

Modafinil should be withdrawn in patients who experience a rash or psychiatric symptoms

For more information about sleep disorders, see:
Rolden G and Ang RC. *Respir Care Clin N Am* 2006; **12:** 31–54, viii.

Modafinil (Provigil ▼) is indicated for the symptomatic relief of excessive sleepiness associated with: narcolepsy, obstructive sleep apnoea/hypopnoea syndrome (OSAHS), and moderate to severe chronic shift work sleep disorder (SWSD).

After a review of clinical trial data and spontaneous reports of suspected adverse drug reactions, product information for modafinil has been updated with information about the risk of serious skin reactions and psychiatric symptoms.

Serious skin reactions

Stevens Johnson Syndrome, erythema multiforme, and toxic epidermal necrolysis have been reported in association with modafinil. These conditions usually occurred within the first 5 weeks of treatment, although there have been isolated cases after more than 3 months' treatment. In clinical trials, the risk of rash resulting in discontinuation of modafinil treatment was higher in children than adults (0·8% *vs* no cases). Modafinil is not authorised for use in children.

Psychiatric symptoms

Suicidal ideation, hallucinations, delusion, aggression, psychosis, and mania have been reported in association with modafinil. These reactions have occurred mainly, *but not exclusively*, in patients with a history of psychosis, depression, or mania.

See also a letter sent to healthcare professionals in February 2008.
http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/index.htm

Advice for healthcare professionals:

- Modafinil should be discontinued at the first sign of rash and not restarted
- Modafinil should be discontinued in patients who experience any psychiatric symptoms and not restarted
- Modafinil should be used with caution in patients with a history of psychosis, depression, or mania
- Modafinil should be used with caution in patients with a history of alcohol, drug, or illicit substance abuse

Yellow Card scheme update

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

Yellow Card Centres—important contribution to drug safety

There are five Yellow Card Centres in the UK, which have a role in follow-up of reports, communication, and provision of information and education for both healthcare professionals and patients about adverse drug reactions (ADRs) and how to report them (see table).

Yellow Card Centre	Location	Centre Head	Head pharmacist	Webaddress	Contact
Mersey	Pharmacy Practice Unit, Liverpool	Prof Munir Pirmohamed	Justine Howard and Christine Randall	http://www.liv.ac.uk/~druginfo/csm/	druginfo@liv.ac.uk 0151 794 8117
Northern and Yorkshire	Regional Drug & Therapeutics Centre, Newcastle	Dr Simon Thomas	Ros Prior	http://www.nyrdtc.nhs.uk/Services/adr_mon/adr_mon.html	YCCNorthernandYorkshire@nuth.nhs.uk 0191 260 6181
Scotland	Centre for Adverse Reactions to Drugs, Royal Infirmary of Edinburgh	Prof Nick Bateman	Melinda Cuthbert	http://www.ycscotland.scot.nhs.uk/	YCCScotland@luht.scot.nhs.uk 0131 242 2925
Wales	Department of Pharmacology, Therapeutics and Toxicology, Cardiff University	Prof Phil Routledge	Fiona Woods	http://www.yellowcardwales.org/	YCCWales@cardiffandvale.wales.nhs.uk 02920 744181
West Midlands	City Hospital, Birmingham	Prof Robin Ferner	Anthony Cox	http://www.ycwm.org.uk/	help@yccwm.org.uk 0121 507 5672

The roles of Yellow Card Centres are:

- Encouragement of Yellow Card reporting through provision of a local contact point
- Follow-up of Yellow Card reports on behalf of the MHRA
- Continued education and training about ADR reporting for healthcare professionals
- To increase patient awareness of ADR reporting
- Research in field pharmacovigilance and ADRs (where appropriate in partnership with local organisations or reporters)

The centres are staffed by a multidisciplinary team of physicians, pharmacists, and medicines-information scientists who advise on how best to promote awareness and share good practice for ADR reporting.

The importance of Yellow Card Centres was highlighted in the 2004 Report of an Independent Review of Access to the Yellow Card Scheme (London: The Stationary Office), which recommended that their educational potential could be further exploited to increase understanding of the Yellow Card scheme. You can find out more about individual Yellow Card Centres by clicking on their webaddresses in the table; these also offer reporting tips and definitions.

Centres may offer local seminars and lectures. They may also publish newsletters and bulletins for healthcare professionals in their region about ADR reporting and drug-safety issues.

Hot topic

Nasal decongestants that contain pseudoephedrine or ephedrine: update on sales restrictions

Pseudoephedrine and ephedrine are nasal decongestants used either alone or in combination with analgesics or other active ingredients for the symptomatic relief of colds, influenza, and other similar conditions. Most products are available as P medicines (ie, available over-the-counter, OTC, in pharmacies), and some are available only by prescription (ie, POM). A range of pack sizes are available for solid-dose forms and liquid formulations.

See *Drug Safety Update*, November 2007, p 9.
www.mhra.gov.uk/mhra/drugsafetyupdate

The MHRA implemented restrictions last year because of increasing concern about the potential for pseudoephedrine and ephedrine to be extracted from OTC products and used in the illegal manufacture of the Class A controlled drug methylamphetamine (crystal meth).

The following restrictions are in place:

- Small packs of products that contain no more than 720 mg pseudoephedrine (the equivalent of 12 tablets or capsules of 60 mg, or 24 tablets or capsules of 30 mg) may be purchased from retail pharmacies
- Small packs that contain no more than 180 mg ephedrine may be purchased from retail pharmacies
- A limit of one equivalent pack per customer per purchase

Products that contain more than 720 mg pseudoephedrine or 180 mg ephedrine

For further information about the consultation, see
http://www.mhra.gov.uk/Publications/Consultations/Medicinesconsultations/MLXs/CON2032570

The sale and supply of products that contain more than 720 mg pseudoephedrine and 180 mg ephedrine will be subject to prescription control. This follows a positive opinion on proposals set out in a public consultation that invited comment on tighter sales restrictions for nasal decongestant products that contain pseudoephedrine or ephedrine.

See also
http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON2033608

The Commission on Human Medicines advised that the sale and supply of products that contain more than 720 mg pseudoephedrine and 180 mg ephedrine should be subject to a prescription from an appropriately qualified medical practitioner. Legislative measures will be implemented from April 1, 2008 and will underpin the voluntary restrictions already in place.

Continued monitoring

The Commission has set up a working group to advise on the practical introduction of these recommendations and to monitor the effect of these controls. This group is currently reviewing the risks and benefits associated with all decongestants in this class compared with alternative treatments to ensure that the benefits of these medicines outweigh the potential risk to the public from their illicit use.

The Commission's advice remains: all products that contain pseudoephedrine or ephedrine should be reclassified from P to POM status in 18 months' time (ie, in 2009), or earlier if necessary, unless the new sales restrictions contain the risk to the public from the misuse of these medicines.

Stop press

Boots' Medisure Domiciliary Dosage System (DDS): risk of incorrect dose

For further information, please contact the MHRA on 01253 596 000, quoting reference 2007/011/012/061/009.

Boots Pharmacies use the Medisure Domiciliary Dosage System (DDS) as a medication-packaging method designed to help individuals take the correct medicine at the prescribed dose at the correct time.

We have been made aware of a patient who took the incorrect dose of their medication because the individual compartments of the Medisure DDS had not been sealed fully, allowing the tablets or pills to migrate between individual compartments. No harm was reported, but in different circumstances and with different medication there is potential for serious consequences to a patient's health.

Boots have stated that they are not aware of any similar incidents and we have received no other reports to date. To reduce the potential for a repeat incident, Boots have highlighted this problem to their pharmacy staff via a bulletin and are revising their procedures to include the need for more stringent checks (physical and visual) on the pack seal to prevent tablet or pill migration. The Boots bulletin also emphasises the need to use a roller together with appropriately sized blister packs and platens.

For details on how to report adverse incidents involving medical devices or aids for daily living, see http://www.mhra.gov.uk/Safetyinformation/Reportingsafetyproblems/Devices/index.htm

Please report to us any similar adverse incidents with monitored dose systems.

Recent letters to healthcare professionals

Letters to healthcare professionals are updated monthly on our website. See: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/index.htm

In February 2008, letters sent from Marketing Authorisation Holders to healthcare professionals included updated safety information for: **mycophenolate mofetil** (CellCept, reports of progressive multifocal leukoenecephalopathy) and **alemtuzumab** (MabCampath, six infection-related deaths in clinical trial of fludarabine and rituximab treatement followed by alemtuzumab for remission consolidation).

New electronic Yellow Card launched

Go to to www.yellowcard.gov.uk to access the new and improved electronic Yellow Card for the reporting of suspected adverse drug reactions. Find out more in next month's *Drug Safety Update.*

Other information from the MHRA

Injectable medicines for cosmetic procedures: supply and administration

For information on the safety of Botox, see *Drug Safety Update*, October 2007 p 10; www.mhra.gov.uk/mhra/drugsafetyupdate

We have recently published updated guidance on the supply and administration of Botox, Vistabel, Dysport, and other injectable medicines that are used in cosmetic procedures.

Access the guidance on our website at http://www.mhra.gov.uk/Howweregulate/Medicines/Availabilityprescribingsellingandsupplyingofmedicines/Frequentlyraisedissues/BotoxVistabelDysportandotherinjectablemedicinesincosmeticprocedures/index.htm

The guidance gives information on the circumstances by which some healthcare professionals can prescribe and administer these medicines, including nurse independent prescribers.

Earlier access to medicines

Access the Ministerial Industry Strategy Group report at http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON2033873

The Cooksey review is available at http://www.hm-treasury.gov.uk./independent_reviews/cooksey_review/cookseyreview_index.cfm

The Ministerial Industry Strategy Group, a partnership between representatives from government and the pharmaceutical industry, held a forum in September 2007 to debate the feasibility of making medicines available at an earlier stage of their development. This recommendation was made by Sir David Cooksey in his 2006 Review of Health Research Funding. The Group recommended that earlier access to medicines could benefit patients in some circumstances—read more about the forum on our website.

Patient Information Leaflet of the month

Access PIL of the month at http://www.mhra.gov.uk/Howweregulate/Medicines/Labelspatientinformationleafletsandpackaging/Patientinformationleaflet(PIL)ofthemonth/index.htm

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 Nicorette Microtabs used in nicotine-replacement therapy for smoking cessation. This PIL is a booklet rather than a flat leaflet and has some important navigation tools in the information design.

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

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