

Drug Safety Update



Latest advice for all medicines users

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

Volume 2, Issue 3 **October 2008**

Contents

Click on text to go to page

Drug safety advice	Ergot-derived dopamine agonists: risk of fibrotic reactions in chronic endocrine uses	2
	Use of antibiotics in premature labour: latest information	3
Yellow Card Scheme update	When to report an adverse drug reaction	5
Hot topic	Pseudoephedrine and ephedrine nasal decongestants: risk of illicit use	6
Stop press	Theophylline: narrow therapeutic index and potential for misuse	8
Other information from the MHRA	Central Alerting System: access to urgent safety guidance	8
	Patient Information Leaflet of the month: Livial (tibolone)	8
	Unlicensed medicines: latest imports	9
	Consultation: dispensing opticians and access to prescription medicines	9

Many of you who prescribe or encounter ergot-derived dopamine agonists in practice will be aware of the recent new warnings and contraindications as a result of the risk of fibrosis, particularly cardiac fibrosis, associated with chronic use (see Drug Safety Update July 2008, p 9). In addition to their indications for Parkinson's disease, the ergots cabergoline and bromocriptine are also indicated for the treatment of chronic endocrine disorders. If you manage patients with these disorders, please read our guidance on p 2.

Also this month, important information for community pharmacists. Please continue to remain vigilant about sales of pseudoephedrine and ephedrine nasal decongestants. We have further evidence of their illicit use in the manufacture of the Class A drug methylamphetamine (p 6). We also ask community pharmacists to please check whether patients who buy the bronchodilator theophylline without a prescription are also taking any other medicines (including theophylline on prescription; p 8). Theophylline interacts with several medicines and has a narrow margin of safety between therapeutic and toxic doses. It may also be misused by some patients—particularly in combination with ephedrine.

The Yellow Card Scheme update this month (p 5) reminds you that the Scheme is simply a way to report your suspicion that a medicine or vaccine might have caused an adverse reaction. Please do not be put off from reporting because you are not absolutely certain about cause and effect. Your report will be looked at in the context of any other relevant information and it can add to our knowledge and understanding.

If in doubt, please report.

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 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

Ergot-derived dopamine agonists: risk of fibrotic reactions in chronic endocrine uses

Keywords: ergot-derived dopamine agonists, cabergoline, bromocriptine, endocrine disorders, hyperprolactinaemia, fibrosis, cardiac valvulopathy

Chronic use of ergot-derived dopamine agonists is associated with a risk of fibrosis, particularly cardiac fibrosis. Cardiac valvulopathy should be excluded by echocardiography before treatment with cabergoline or bromocriptine. Patients should be monitored during treatment as outlined below

The European Medicines Agency has recommended new warnings and contraindications for ergot-derived dopamine agonists as a result of the risk of fibrosis, particularly cardiac fibrosis, associated with chronic use. The risk of cardiac fibrosis is higher with cabergoline and pergolide than with the other ergot-derived dopamine agonists.

Cabergoline, pergolide, and bromocriptine are indicated for the treatment of Parkinson's disease. Key advice on new warnings, contraindications, dose, and side-effects has previously been provided for this indication.

Cabergoline (brand leader Dostinex) is used in hyperprolactinaemia. The recommended initial Dostinex dose for this indication is 0.5 mg a week, given in one or two doses a week and titrated according to prolactin levels; therapeutic dose is usually 1 mg a week. Bromocriptine (brand leader Parlodel) is indicated for chronic endocrine disorders such as hyperprolactinaemia and acromegaly. For dosing information, refer to the Summaries of Product Characteristics. This new advice applies only to treatment of chronic endocrine disorders with these agents—it does not apply to the inhibition of lactation.

Advice for healthcare professionals:

Cabergoline and bromocriptine

- Exclude cardiac valvulopathy as determined by echocardiography before treatment
- Monitor patients for signs or symptoms of pleuropulmonary disease (eg, dyspnoea, shortness of breath, persistent cough, or chest pain) and retroperitoneal disorders during treatment. Renal insufficiency or ureteral or abdominal vascular obstruction might occur, with pain in the loin or flank and leg oedema. Abdominal masses or tenderness could suggest retroperitoneal fibrosis

Cabergoline

- Monitor patients for signs of cardiac fibrosis during treatment
- Echocardiography should be done within 3–6 months of starting treatment and subsequently at 6–12-month intervals
- Stop treatment if echocardiography shows new or worsened valvular regurgitation, valvular restriction, or valve leaflet thickening
- Pregnancy should be excluded before administration of cabergoline
- Women who are planning pregnancy should stop taking cabergoline 1 month before they try to conceive

See *Drug Safety Update* July 2008, p 9;
www.mhra.gov.uk/mhra/drugsafetyupdate

Access Summaries of Product
Characteristics at
<http://emc.medicines.org.uk/>

Further information is available at:
<http://www.emea.europa.eu/pdfs/human/press/pr/32239508en.pdf>

Use of antibiotics in premature labour: latest information

Keywords: co-amoxiclav, erythromycin, ORACLE Children Study, premature rupture of membranes, spontaneous premature labour, cerebral palsy

In the ORACLE Children Study—a 7-year follow-up of a large randomised, placebo-controlled trial to investigate the effects of erythromycin and co-amoxiclav in premature labour—parents reported small increases in the number of children with mild functional impairment or cerebral palsy born to mothers whose membranes were intact and who had received antibiotics. This finding requires further study. Antibiotics save lives, and pregnant women with possible or obvious infections must be considered for treatment with antibiotics

Original ORACLE trial^{1,2}

The ORACLE clinical trial (conducted between 1994 and 2000) aimed to find out whether premature labour may be linked to underlying symptomless maternal infection that could be treated with antibiotics. It recruited two groups of women in premature labour: those whose membranes had ruptured (premature rupture of the membranes)¹ and those whose membranes remained intact (spontaneous premature labour).² Women were not recruited if they had any evidence of infection.

Two antibiotics commonly used in pregnancy at that time (erythromycin and co-amoxiclav) were studied against the effect of a placebo, individually and in combination.

In women whose membranes had ruptured prematurely, prophylactic erythromycin significantly reduced the number of singleton babies born with the primary composite outcome of death, chronic lung disease, or major cerebral abnormality on ultrasonography before discharge. Erythromycin also increased slightly the interval between membrane rupture and delivery, and it decreased maternal infection. However, in these women prophylactic co-amoxiclav increased the risk of neonatal necrotising enterocolitis.

Mainly as a result of these findings the Royal College of Obstetricians and Gynaecologists (RCOG) issued guidance recommending the routine use of erythromycin in women with premature rupture of membranes. Co-amoxiclav is not recommended for use in pregnancy unless considered essential.

In women who presented with spontaneous premature labour without rupture of the membranes, prophylactic antibiotics had neither beneficial nor harmful short-term effects for babies. The RCOG guidance does not advocate the use of antibiotics for women who may be going into premature labour, but who have intact membranes and no obvious infection.

ORACLE Children Study^{3,4}

Almost 6500 of the children born to UK women who participated in the original ORACLE trial were followed up after 7 years by use of a parental questionnaire. In the group with premature rupture of the membranes,³ neither erythromycin nor co-amoxiclav provided long-term benefit or harm to the women or their children. In the group⁴ who had presented with spontaneous premature labour and intact membranes a small increase in the number of children with functional impairment was reported in those whose mothers had received erythromycin, either on its own or with co-amoxiclav. In this group 42.3% of children had some form of functional impairment, mostly mild, compared with 38.3% of children whose mothers had not received any erythromycin.

1 Kenyon SL, et al. *Lancet* 2001; 357: 979–88.

2 Kenyon SL, et al. *Lancet* 2001; 357: 989–94.

3 Kenyon S, et al. *Lancet* published online Sept 18, 2008. DOI: 10.106/S0140-6736(08)61202-7 (www.thelancet.com).

4 Kenyon S, et al. *Lancet* published online Sept 18, 2008. DOI: 10.106/S0140-6736(08)61203-9 (www.thelancet.com).

Has your colleague seen this bulletin?

Access RCOG guidance at
<http://www.rcog.org.uk/index.asp?PageID=1813>

See letter from the Chief Medical Officer at
<https://www.cas.dh.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=219>
and Oracle Children Study website at
<http://www.le.ac.uk/cm/rs/oracle/>
NHS Direct: <http://www.nhsdirect.nhs.uk/>
and
<http://www.nhsdirect.nhs.uk/articles/article.aspx?articleId=2557>

In this group, a small but statistically significant increase in numbers of children with cerebral palsy was also reported. In mothers who had any erythromycin (on its own or together with co-amoxiclav) 3.3% of children had cerebral palsy compared with 1.7% of children whose mothers did not have erythromycin. In those who had co-amoxiclav (on its own or together with erythromycin), 3.2% of children had cerebral palsy compared with 1.9% of children whose mothers did not have co-amoxiclav. The increase in the number of children with cerebral palsy was clearest in the group of women who had both antibiotics (co-amoxiclav and erythromycin together), although the numbers were still small. In this group, 4.4% of children had cerebral palsy, compared with 1.6% of children whose mothers who had received placebo.

Current guidance

Spontaneous premature labour—current guidance does not advocate the use of antibiotics for women who may be going into premature labour, but who have intact membranes and no obvious infection.

Premature rupture of membranes—prophylactic use of erythromycin is recommended in women with premature rupture of membranes and no obvious infection.

Advice for healthcare professionals:

- This research was conducted in a very specific group of women and so the results do not mean that antibiotics are generally unsafe for use in pregnancy. Untreated infections can be dangerous and potentially life-threatening for pregnant women and their unborn babies, and antibiotics should continue to be prescribed in line with current guidance and the product licence
- The study confirms existing practice that antibiotics should not be given routinely to women who are in premature labour with intact membranes and who have no obvious infection
- These results were unexpected and the mechanism by which this reported association occurred in women with intact membranes is unclear, particularly as no increase in functional impairment or cerebral palsy was reported in the children of mothers who received the same antibiotics but whose membranes had ruptured. Additional research is required to shed light on these findings

Further information can be obtained from NHS Direct, the Oracle Children Study website, and a letter from the Chief Medical Officer.

Yellow Card Scheme update

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

When to report an adverse drug reaction

The Yellow Card Scheme is an early warning system for the identification of previously unrecognised adverse drug reactions (ADRs), and for changing information about known ADRs. The continued success of the Scheme depends on your vigilance and willingness to report suspected ADRs. Every report can make a difference.

A better understanding of ADRs allows us to give advice on how medicines can be used more safely. If you suspect that a reaction experienced by your patient is associated with a medicine (or combination of medicines) they are, or have been, taking then you should report it on a Yellow Card.

Please do not be put off from reporting because you are not absolutely certain about cause and effect. You can, however, consider several factors when judging whether a patient may have had a reaction to a medicine:

Nature of reaction

Some clinical events should particularly raise suspicion of an ADR, such as:

- liver dysfunction
- blood dyscrasias
- skin reactions (eg, Stevens-Johnson syndrome or toxic epidermal necrolysis)
- neuroleptic malignant syndrome

Timing

The time from when a patient started taking the medicine to when a reaction develops may be characteristic of the reaction. For example:

- Peripheral neuropathy with linezolid usually occurs after treatment duration longer than the recommended maximum of 28 days
- Psychiatric reactions with steroids usually start within days or weeks of starting treatment

Dose relation

Many ADRs are dose-related and may be apparent after an increase in dose. The effect might be minimised by reducing the dose of the medicine. Symptoms that resolve on stopping the medicine may be associated with it, although they could still be coincidental. If symptoms recur on reintroducing a medicine, it is likely responsible for them. However, deliberate rechallenge may not be justifiable after a serious ADR.

Other possible causes

You may need to consider other possible causes for the symptoms:

- Could the symptoms be manifestations of the patient's underlying illness or another disease?
- Is the patient taking other medicines that could be responsible (including self-medication and herbal remedies)?
- Is there a possibility of an interaction between two medicines?
- Specific investigations or tests may aid diagnosis (eg, plasma drug concentrations, or liver biopsy if drug-induced hepatitis is suspected)

By filling in a Yellow Card you are simply reporting your suspicion. Your report will be looked at in the context of any other information that we have about that particular reaction, and it can therefore add to our knowledge and understanding of the reaction.

If in doubt, please report.

Hot topic

See *Drug Safety Update* March 2008, p 7.
www.mhra.gov.uk/mhra/drugsafetyupdate

Pseudoephedrine and ephedrine nasal decongestants: risk of illicit use

Pseudoephedrine and ephedrine are medicines used as nasal decongestants, which are available from pharmacies. Last year, the MHRA implemented restrictions because of increasing concern about the potential for pseudoephedrine and ephedrine to be extracted from over-the-counter products and used in the illegal manufacture of the Class A controlled drug methylamphetamine (crystal meth).

The following legal restrictions were put in place from April 1, 2008:

- 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

Evidence of illicit use

The Serious Organised Crime Agency has informed us that a methylamphetamine lab has been recently found in the London area. About 100 empty packs of single-constituent pseudoephedrine tablets were found, and one person has been arrested.

Pseudoephedrine and ephedrine must be sold in line with the recent change in the law:

- It is illegal to sell or supply any product that contains more than 720 mg pseudoephedrine or 180 mg ephedrine without a prescription
- It is illegal to sell or supply a combination of products that between them add up to more than 720 mg pseudoephedrine or 180 mg ephedrine without a prescription
- It is illegal to sell or supply a product that contains pseudoephedrine and a product that contains ephedrine in one transaction

Advice for pharmacists:

- Please brief your healthcare team on this recent incident of illicit use
- Ensure all requests for more than one pack of a product that contains pseudoephedrine or ephedrine are referred to a pharmacist
- Report any suspicious activity in line with guidance from the Royal Pharmaceutical Society of Great Britain—see below

Printed below (with permission) is the “*Look, listen, report your suspicions*” card from the RPSGB and the Commission on Human Medicines Working Group on Pseudoephedrine/Ephedrine:

Pseudoephedrine and ephedrine

Pseudoephedrine and ephedrine products have been purchased from UK pharmacies and used in the illegal manufacture of an intensely addictive and dangerous Class A drug called methylamphetamine (also known as meth or crystal meth).

Of course, the person attempting to make a dishonest purchase may not be a user. In fact, experience from around the world tells us these people are rarely users. They may be male or female and of any age or background and therefore it is

important not to be misguided by any stereotypes you might have.

Pharmacists and pharmacy staff are good at telling when a medicine purchase doesn't feel quite right, so use your instincts. As well as asking for multiple packs, or making regular, repeat purchases, here are some things that might make you suspicious about someone requesting pseudoephedrine or ephedrine.

When asked for a medicine containing pseudoephedrine or ephedrine you should:

LOOK, LISTEN, REPORT YOUR SUSPICIONS

LOOK

Does the customer –

- ▲ **Appear nervous or guilty** (eg, unable to make eye contact or uncomfortable answering questions)?
- ▲ **Have no obvious symptoms of cough, cold or flu?**
- ▲ **Seem impatient or in a hurry to complete the transaction** (eg, having the correct money ready)?
- ▲ **Act in an aggressive manner and stance or alternatively speak quietly?**
- ▲ **Manipulate the environment to improve the chances of a successful purchase** (eg, waiting until the shop is busy or until younger or less senior staff are available)?

LISTEN

Does the customer –

- ▲ **Ask for products for someone else without being able to describe their symptoms?**
- ▲ **Give answers to questions that appear rehearsed?**
- ▲ **Ask for specific products by name** (particularly those containing only pseudoephedrine or ephedrine)?
- ▲ **Only want to buy liquid or combination products if tablets and capsules are not available?**
- ▲ **Attempt to purchase other products** (eg, lithium batteries) or **chemicals** (eg, acetone) **that could be used in the manufacture of methamphetamine?**

REPORT YOUR SUSPICIONS

What should you do?

- ✓ Individually these behaviours may not be suspicious, but when occurring together they are strong grounds for suspicion. Your report may be an important piece of information that can help stop a local methylamphetamine problem from escalating.
- ✓ If you are suspicious, **REPORT YOUR SUSPICIONS** to your area Royal Pharmaceutical Society Inspector.
- ✓ Before reporting your suspicions, make a note of what the customer looked like, what they were wearing and any notable features about them.
- ✓ Consider warning neighbouring community pharmacies about the customer.



Published by the Royal Pharmaceutical Society of Great Britain. Contact details for the Society's inspectors can be accessed via www.rpsgb.org or tel 020 7572 2308.

April 2008

Stop press

Theophylline: narrow therapeutic index and potential for misuse

Several products that contain **theophylline** or **aminophylline** are available as pharmacy medicines that can be dispensed without a prescription. Theophylline—a bronchodilator—interacts with several medicines and has a narrow margin of safety between therapeutic and toxic doses. Therefore, community pharmacists are reminded to check whether patients who buy theophylline without a prescription are also taking any other medicines (including theophylline on prescription).

Theophylline may be misused by some patients—particularly in combination with ephedrine. For instance, Do-Do ChestEze tablets contain theophylline, caffeine, and ephedrine. It is important to note that the theophylline content of these tablets is potentially toxic if misused, especially if taken with other medicines.

Please report any suspected adverse reactions or suspected cases of misuse of theophylline via a Yellow Card (see www.yellowcard.gov.uk).

For further information on medicines that interact with theophylline, see Summaries of Product Characteristics at <http://emc.medicines.org.uk/>

Other information from the MHRA

Central Alerting System: access to urgent safety guidance

In September 2008, the Department of Health launched a new web-based system to enable healthcare professionals to access urgent and important safety guidance. The Central Alerting System (<https://www.cas.dh.gov.uk/Home.aspx>) hosts safety information issued by the MHRA, Chief Medical Officer, Department of Health, and the National Patient Safety Agency.

The Central Alerting System replaces the Chief Medical Officer's Public Health Link and the Safety Alert Broadcast System. When a new alert is issued, key personnel will be notified by email. They may be instructed to cascade the information to colleagues. Those who received alerts through the Public Health Link and Safety Alert Broadcast System will continue to do so through the new Central Alerting System.

You can use the Central Alerting System to view and search new alerts, as well as past alerts that were issued through the Public Health Link and Safety Alert Broadcast System. Further information is available at <https://www.cas.dh.gov.uk/Home.aspx>.

Patient Information Leaflet of the month: Livial (tibolone)

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 enable 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 the PIL for **Livial** (tibolone), which is indicated for short-term treatment of symptoms of oestrogen deficiency.

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

Unlicensed medicines: latest imports

Access the report at
<http://www.mhra.gov.uk/Howweregulate/Medicines/Medicinesregulatorynews/CON023191>; procurement advice for melatonin is available at
<http://www.mhra.gov.uk/NewsCentre/CON023251>

Where they exist, licensed products should be used in preference to those that are unlicensed.

The MHRA considers notifications for importation of unlicensed medicines to meet a special clinical need. You may be interested to read our latest summary report on imports for the period April 1–June 30, 2008.

The report lists the 50 most common imported medicines notified to the MHRA. **Melatonin** products were the most common import. However, at the beginning of June 2008, a licensed modified-release melatonin product (Circadin ▼) became available in the UK. We therefore advise that this licensed product is used whenever possible because imported melatonin may be of non-pharmaceutical grade from the USA, where it is classed as a supplement rather than a medicine.

Consultation: dispensing opticians and access to prescription medicines

To respond to the consultation by Nov 28, 2008, and to read further information see
<http://www.mhra.gov.uk/Publications/Consultations/Medicinesconsultations/MLXs/CON025637>

We have launched a consultation to seek views on amendments to allow dispensing opticians access to some prescription-only medicines (POMs). The proposals would enable dispensing opticians to order stocks of specified POMs and to administer them in certain circumstances. The intent is to address a practical difficulty when there is insufficient stock in practices for use by visiting optometrists, and to enhance patient care by reflecting developments in contact-lens practice.

Read more about the Commission on Human Medicines, including summaries of minutes from meetings, at
<http://www.mhra.gov.uk/mhra/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 <http://www.yellowcard.gov.uk>