Drug Safety Update

Latest advice for all medicines users

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

Volume 2 Issue 10 **May 2009**

Contents

Click on text to go to page

Antihypertensive medicines feature in this month's Drug Safety Update. Read the recommendations on the use of ACE inhibitors and angiotensin II receptor antagonists during breastfeeding (p 3). Furthermore, we have advice for the first-in-class renin inhibitor aliskiren (Rasilez▼).

Angioedema may occur with aliskiren, and it should therefore not be used in patients who have previously had angioedema after using it. We would also like to remind you of the potential adverse renal effects associated with aliskiren when used in at-risk patients. Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) may reduce aliskiren's antihypertensive effect and may result in further renal deterioration in those with compromised renal function (p 4). Furthermore, page 4 has a reminder on the use of NSAIDs alone in patients with established, or a risk of, renal failure as we continue to receive case reports of renal failure and impairment with NSAID use.

Also this month, our Hot topic highlights the key safety information that pharmacists should consider when supplying orlistat. This medicine, under the brand name alli, is now available in pharmacies as a non-prescription medicine to aid weight loss in conjunction with a reduced-calorie, lower-fat diet (p 6).

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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 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

Aliskiren (Rasilez▼): risk of angioedema and renal dysfunction

Keywords: aliskiren, angioedema, essential hypertension, high blood pressure, NSAIDs, Rasilez▼, renal artery stenosis, renal dysfunction, renal failure, tissue swelling

Angioedema may occur with use of aliskiren (Rasilez ▼), and it should not be used in patients who have previously had angioedema after using it. Aliskiren should be used with caution in patients taking NSAIDs, or in patients who may be at increased risk of acute renal failure such as patients with renal artery stenosis or with risk factors for renal dysfunction

Aliskiren (Rasilez▼) is the first of a new class of medicine that directly inhibits renin. Aliskiren is used for the management of high blood pressure, at a recommended dose of 150 mg once daily; in patients whose blood pressure is not adequately controlled, the dose may be increased to 300 mg once daily.

Angioedema

Angioedema (a serious allergic reaction that causes swelling of the face or throat and occasionally other areas such as the hands) can occur as a rare and serious side-effect of treatment with aliskiren. It can develop rapidly, and can be dangerous if it affects the throat because it can lead to obstruction of the airway.

See also information from the European Medicines Agency at http://www.emea.europa.eu/pdfs/human/press/pr/8952309en.pdf

Acute renal failure

There have been reports of acute renal failure in patients with risk factors for renal dysfunction (including hypovolaemia, heart disease, liver disease, or kidney disease). Furthermore, there is an increased risk of renal insufficiency, including acute renal failure, when patients with renal artery stenosis are treated with aliskiren.

Use with NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) may reduce the antihypertensive effect of aliskiren. In some patients with compromised renal function (eg, dehydrated or elderly patients) aliskiren given concomitantly with NSAIDs may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible when treatment is stopped.

Has your colleague seen this bulletin?

Advice for healthcare professionals:

- Aliskiren should not be used for the management of high blood pressure in patients who have previously had angioedema when using it
- Patients should be advised that they should stop aliskiren and seek medical advice straight away if they develop symptoms of angioedema, such as swelling of the face, eyes, lips or tongue (or both), hands and feet, or difficulty breathing or swallowing
- Extreme caution is required if aliskiren is used in patients with renal artery stenosis or conditions predisposing to kidney dysfunction (such as hypovolaemia, heart disease, liver disease, or kidney disease) because of a risk of acute renal failure. If any signs of renal failure occur, aliskiren should be promptly discontinued
- NSAIDs may reduce the antihypertensive effect of aliskiren
- Elderly patients or patients with compromised renal function may be at risk of further deterioration of renal function if NSAIDs and aliskiren are used together

ACE inhibitors and angiotensin II receptor antagonists: recommendations on use during breastfeeding

Keywords: ACE inhibitors, angiotensin II receptor antagonists, breastfeeding, lactation, pregnancy

ACE inhibitors and angiotensin II receptor antagonists should not be used by breastfeeding mothers in the first few weeks after delivery because of possible profound neonatal hypotension; preterm babies may be at particular risk. In mothers who are breastfeeding older infants, the use of captopril, enalapril, or quinapril may be considered

See Drug Safety Update December 2007, p 8; www.mhra.gov.uk/mhra/drugsafetyupdate

Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists are licensed for a range of conditions including hypertension and may be particularly suitable for young patients with high blood pressure (but not those of black ethnic origin) and those with some comorbidities such as diabetic nephropathy.

Methyldopa is recognised to be the antihypertensive of choice during pregnancy and breastfeeding, but will not be suitable for some women and other options may need to be explored.

Use in pregnancy: reminder

Angiotensin II is essential for normal kidney development, and the use of ACE inhibitors and angiotensin II receptor antagonists in late pregnancy has been associated with adverse effects on the kidney and other congenital anomalies. Some data have also suggested an increased risk of congenital anomaly after exposure during the first trimester of pregnancy.[1] Therefore, ACE inhibitors and angiotensin II receptor antagonists should not be used at any stage of pregnancy unless absolutely necessary, and only then after the potential risks and benefits have been discussed with the patient.

1 Cooper WO, et al. *N Engl J Med* 2006; **354:** 2443–51.

Use during breastfeeding

ACE inhibitors

In general, ACE inhibitors have a small molecular size and so their transfer to breast milk is possible. With the exception of captopril, the active metabolites of ACE inhibitors have long elimination half-lives; however, these metabolites are poorly absorbed orally. Data on the use of ACE inhibitors in breastfeeding are sparse and relate mostly to captopril, enalapril, and quinapril; findings indicate that drug is transferred to breast milk.[2–4] Although the levels transferred to an infant via breastfeeding are unlikely to be clinically relevant, there are insufficient data to exclude a possible risk of profound neonatal hypotension, particularly in preterm babies.

2 Devlin RG and Fleiss PM. *J Clin Pharmacol* 1981; **21:** 110–13.

3 Redman CW, et al. *Eur J Clin Pharmacol* 1990; **38:** 99.

4 Begg EJ, et al. *Br J Clin Pharmacol* 2001; **51:** 478–81.

Angiotensin II receptor antagonists

No data on the use of angiotensin II receptor antagonists are available. These agents are also small enough to pass into breast milk, and some unpublished studies have found them in the milk of lactating rats. However, most angiotensin II receptor antagonists are highly bound to maternal plasma proteins, which can substantially limit their transfer into breast milk. The effects of potential exposure on a nursing infant are unknown.

Advice for healthcare professionals:

ACE inhibitors:

- Captopril, enalapril, or quinapril: use in breastfeeding is not recommended in the first few weeks after delivery because of the possibility of profound neonatal hypotension; preterm babies may be at particular risk. Use may be considered when the infant is older if an ACE inhibitor is necessary for the mother; careful follow-up of the infant for possible signs of hypotension is recommended

Continues...

- **Ramipril, lisinopril, fosinopril, trandolapril, moexipril, or perindopril**: use in breastfeeding is not recommended. Alternative treatments with more established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm baby

All angiotensin II receptor antagonists:

- Use in breastfeeding mothers is not recommended. Alternative antihypertensive treatments with more established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm baby

Non-steroidal anti-inflammatory drugs: reminder on renal failure and impairment

Keywords: non-steroidal anti-inflammatory drug, NSAID, renal failure, renal impairment, hypovolaemia, congestive heart failure, liver cirrhosis, multiple myeloma

Caution should be exercised when using NSAIDs in patients with established, or a risk of, renal impairment

Non-steroidal anti-inflammatory drugs (NSAIDs, including COX-2 inhibitors) may rarely precipitate renal failure, and vulnerable (particularly elderly) patients may be at increased risk. NSAID use accounts for an estimated 15% of all cases of drug-induced acute renal failure.[1] A case-control study estimated an increased relative risk (3·2 [95% CI 1·8–5·8]) of acute renal failure in otherwise healthy current users of NSAIDs.[2]

We continue to receive case reports of renal failure in NSAID users. Prescribing information for NSAIDs includes warnings about renal impairment and renal failure, and advises that the risk of renal failure is highest in those with existing renal impairment.

In patients with conditions that cause renal hypoperfusion, prostaglandin production may be increased to maintain adequate renal blood flow. The adverse renal effects associated with NSAIDs are mainly mediated via inhibition of prostaglandin-induced vasodilation and can result in reduced renal blood flow. Patients with conditions such as hypovolaemia, congestive heart failure, liver cirrhosis, or multiple myeloma are at particular risk. Contributing risk factors include the current administration of medicines such as angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptors antagonists, and diuretics.

NSAIDs may also produce direct toxic effects on the kidney. The main mechanisms for acute renal failure include acute tubular necrosis and acute interstitial nephritis. Other rarer mechanisms have also been reported, such as acute papillary necrosis and renal vasculitis. Adverse renal effects are generally reversible on discontinuation of NSAID treatment.

1 Delmas PD. *Br J Rheumatol* 1995; **34** (suppl 1)**:** 25–28.
2 Huerta C, et al. *Am J Kidney Dis* 2005; **45:** 531–39.

Advice for healthcare professionals:

- Patients at risk of renal impairment or renal failure (particularly elderly people) should avoid NSAIDs if possible. If NSAID treatment is absolutely necessary, then the lowest effective dose for the shortest possible duration should be used to control symptoms. The renal function of such patients should be carefully monitored during NSAID treatment
- It is important to consider other concomitant disease states, conditions, or medicines that may precipitate reduced renal function when prescribing NSAIDs

Yellow Card Scheme update

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

See Drug Safety Update November 2008 for information on varenicline (p 2) and on rimonabant (p 8); www.mhra.gov.uk/mhra/drugsafetyupdate

Patient reporting

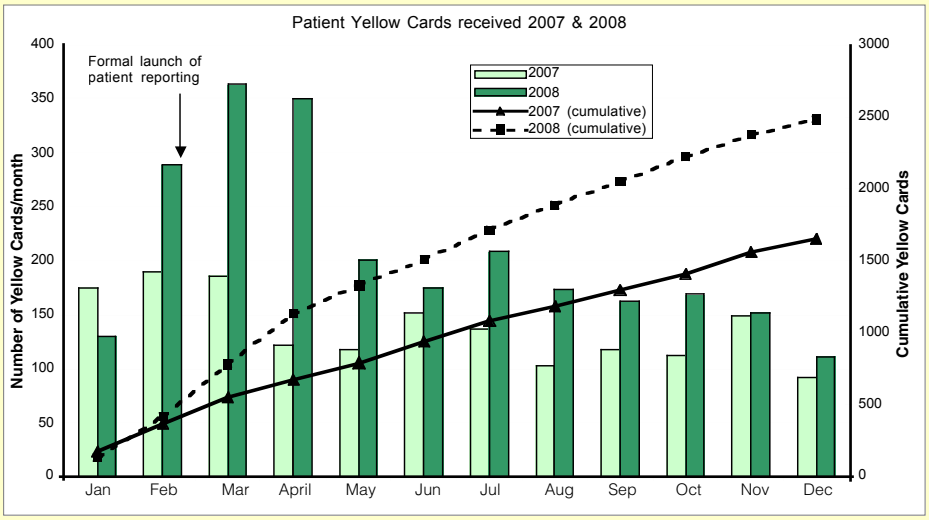
In February 2009, the MHRA celebrated the first anniversary of the establishment of patient reporting as a part of the Yellow Card Scheme; it also marked 1 year since the introduction of a new online Yellow Card reporting system, both of which were launched through a publicity campaign in community pharmacies.

The Yellow Card Scheme is a vital part of the Agency's work in drug-safety monitoring. Information collected from the Scheme over the past year has contributed to the Agency's advice on the safety of medicines such as varenicline (Champix ▼, in particular its association with adverse psychiatric reactions), and rimonabant (Acomplia) which was withdrawn from use because of psychiatric risks.

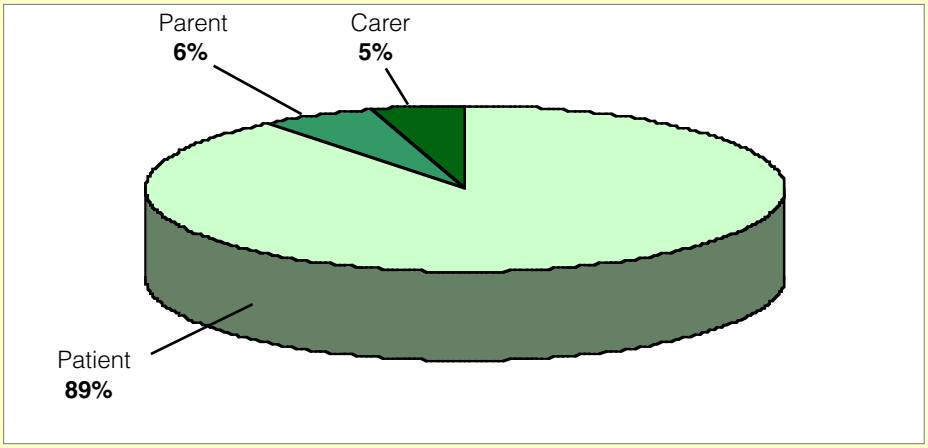
In 2008, more than 2500 Yellow Cards were completed by patients or carers, bringing the total number of patient reports to almost 9000. The Agency has also seen a doubling in the number of reports submitted using the online Yellow Card during 2008.

There has been a 50% increase in reporting from patients and carers and a 17% increase in reporting overall compared with 2007, making a total of more than 25 000 Yellow Cards received from all reporters in 2008. The figures below show further information on patient reporting:

Patient Yellow Cards received 2007 & 2008



Patient Yellow Cards received by reporter type 2008



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Yellow Card Scheme update

continued

The more reports we receive about suspected adverse drug reactions, the earlier we can detect signals of safety issues and promptly communicate important safety messages to healthcare professionals and the public—everyone benefits from earlier and better information.

The success of initiatives to increase awareness of the Yellow Card Scheme has been demonstrated, and work is continuing in this area. We are examining the reasons that may prevent or discourage healthcare professionals from reporting suspected adverse drug reactions, and are working with a number of organisations to make Yellow Card reporting simpler through use of information technology systems in the NHS.

Please continue to send us Yellow Cards of suspected adverse drug reactions and encourage patients to do the same—most easily done at www.yellowcard.gov.uk. The continued success of the Scheme depends on **your** vigilance and willingness to report. Every report can make a difference. If in doubt about cause and effect, please report anyway.

Remember: Don't delay, report today!

Hot topic

Orlistat: key safety information to support pharmacy availability

Pharmacy availability of orlistat

Orlistat is now available in pharmacies (under the brand name alli) as a non-prescription medicine to aid weight loss in conjunction with a reduced-calorie, lower-fat diet. This availability follows a recommendation made by the EU Committee for Medicinal Products for Human Use in October 2008, confirmed by the European Commission in January 2009, that orlistat 60 mg capsules should receive a marketing authorisation and should be available without prescription. Before this decision, orlistat was, and remains, available as 120 mg capsules on prescription only (under the brand name Xenical).

See http://www.emea.europa.eu/humandocs/PDFs/EPAR/alli/4937708en.pdf

Training material for pharmacy staff is available via www.mypharmassist.co.uk

This Hot topic outlines the key safety information that pharmacists should consider when supplying alli.

Mechanism of action

alli is licensed as an aid to weight loss in combination with a reduced-calorie, lower-fat diet. It inhibits gastrointestinal lipases in the digestive system, decreasing the amount of fat absorbed from the diet. Fat that is not absorbed passes through the gut and out of the body naturally in stools. A lower-fat diet is important to aid weight loss and to minimise gastrointestinal side-effects (see below). Patients should adopt this diet before starting alli.

Hot topic *continued*

Printed support materials are available with purchase, and online support is available via the website given on product packaging.

Patients should be aware that alli is not a quick fix to weight loss: it can be used to help someone aim for steady weight loss of 1–2 lbs per week in conjunction with a sustained reduced-calorie, lower-fat diet; increased physical activity will also aid weight loss, and behavioural support should be recommended.

One capsule of alli should be taken before or within 1 hour of the three main meals per day (maximum three capsules per day). alli will only work with fat in the diet, so a capsule should not be taken if there is no fat in the meal. Treatment should not exceed 6 months, and thereafter users should continue with a reduced-calorie, lower-fat diet and activity plan to maintain weight loss.

Potential side-effects

alli is a non-systemic treatment that works in the gut. Therefore, the most common side-effects are gastrointestinal and relate to the drug preventing fat absorption. Compliance with a lower-fat diet will help limit these side-effects. If too much fat is consumed, diet-related treatment effects are more likely and could lead to diarrhoea or increased urgency, and passage of oily stools with or without wind. Cases of rectal bleeding have been reported in patients taking orlistat. If this occurs, the patient should consult a doctor.

Patient eligibility

alli can be recommended for adults (ie, age 18 years or older) who have a body-mass index of ≥28. Users must be ready to follow a reduced-calorie, lower-fat diet.

alli is not suitable for women who are pregnant or breastfeeding. Pharmacists should ensure that patients are not allergic to any of the ingredients in alli, and that they do not have chronic malabsorption syndrome or cholestasis.

Interactions:
Because alli decreases fat absorption, it can affect absorption of fat-soluble drugs and vitamins. Therefore, the actions of the following drugs may be affected:

- ciclosporin—contraindicated with alli treatment
- warfarin and other oral anticoagulants—contraindicated with alli treatment (because of potential for decreased vitamin K absorption)
- amiodarone—patients should see their GP before starting alli as it may be necessary to adjust amiodarone dose

Before starting alli, patients with diabetes should see a GP. alli is not recommended for use by patients who are taking acarbose for diabetes because interaction studies have not been done.

Those who are taking medicines for high blood pressure or high cholesterol should visit their GP while taking alli. Such consultation will ensure patients are taking the correct dose of these medicines.

alli may indirectly reduce bioavailability of the oral contraceptive pill. Patients should be advised to use additional contraception if they have severe diarrhoea.

alli can reduce absorption of fat-soluble vitamins (ie, A, D, E, and K): patients should take a multivitamin supplement at bedtime.

Health check

Patients should be reminded that being overweight increases the risk of developing several serious health problems such as diabetes and heart disease. These conditions may not cause someone to feel unwell so a visit to the GP for a general health check should be encouraged.

Stop press

New advice on oral salicylate gels for those younger than age 16 years

The MHRA has reviewed the safety of oral topical salicylate-containing products after publication of a case report of suspected Reye's syndrome associated with use of a dental gel that contained choline salicylate in a 20-month-old child.[1]

1 Oman TK, et al. *BMJ* 2008; **336**: 1376.

The review concluded that the symptoms were not consistent with Reye's syndrome and were more likely to reflect salicylate toxicity, but nevertheless showed that substantial systemic levels of salicylate were achievable after overuse of salicylate-containing dental gels. The Commission on Human Medicines acknowledged that although there is only a theoretical risk of Reye's, these products should be contraindicated in those younger than age 16 years in line with other oral salicylate-containing preparations. This decision affects four products currently licensed in the UK: Bonjela; Bonjela Cool Mint; Dinnefords Teejel Gel (not marketed); and Pyralvex. In those younger than age 16 years, these products are no longer indicated for pain associated with infant teething, orthodontic devices, cold sores, or mouth ulcers.

Advice for healthcare professionals:

- Please advise parents and patients that those younger than age 16 years should use alternative treatments or products. There are several dental gels available which contain a local anaesthetic/mild antiseptic
- For infant teething, gentle pressure with something cool such as a chilled teething ring may help relieve teething pain
- For pain associated with orthodontic devices, salt water mouthwashes are recommended for sore areas. For discomfort arising from tooth movement, a paracetamol-based painkiller is recommended

Further information on teething is available in the Department of Health's 'Birth to five' (May 2007), available at http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_074924

Further information can be found at: http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON044014

Fortodol: risk of serious liver damage

The Food Standards Agency has issued a warning about the food supplement **Fortodol** (also sold as Miradin), which may contain **nimesulide** (an anti-inflammatory drug that is not authorised in the UK and is associated with a risk of liver damage).

The warning has been issued after information was received from the Swedish Medical Products Agency about 11 cases of liver damage, including a fatal case of liver failure, in Sweden after taking Fortodol; five further cases of liver damage (including a second death) have been reported to the Norwegian Medical Products Agency. To date, no cases have been reported in the UK.

Fortodol and Miradin are sold in the UK and over the internet as food supplements, but are commonly accompanied by illegal and unsubstantiated medicinal claims about relief of arthritis, muscle pains, and headaches.

As a precaution, anyone who is using these products should be advised to stop immediately.

Please remember that suspected adverse reactions to Fortodol or Miradin can be reported via the Yellow Card Scheme at www.yellowcard.gov.uk.

MHRA further information: http://www.mhra.gov.uk/Howweregulate/Medicines/Herbalandhomoeopathicmedicines/Herbalmedicines/HerbalSafetyNews/Currentsafetyissues/CON041393
Food Standards Agency: http://www.food.gov.uk/news/newsarchive/2009/mar/warningunsafefoodsupp
Swedish Medical Products Agency: http://www.lakemedelsverket.se/english/All-news/NYHETER---2009/Serious-hepatic-reactions-associated-with-the-dietary-supplement-Fortodol/

Other information from the MHRA

Patient Information Leaflet of the month: Caverject

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 new initiative, we are publishing a series of examples of best practice on our website. The latest in the series is for **Caverject**, an injectable medicine which contains **alprostadil** and is indicated for treatment of erectile dysfunction. The leaflet includes risk-communication tools and diagrams which in testing patients found helpful.

See http://www.mhra.gov.uk/Howweregulate/Medicines/Labelspatientinformationleaflets andpackaging/Patientinformationleaflet(PIL) ofthemonth/index.htm

MHRA–NICE London study day for doctors in training

A study day is being held in London this month for recently qualified doctors to highlight how critical advice from MHRA and NICE can affect day-to-day practice. Further information is available on our website.

For an outline of the topics covered, visit http://www.mhra.gov.uk/ConferencesLearningCentre/Conferences/CON038859

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

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