

Prepared by the Adverse Drug Reactions Advisory Committee (ADRAC) and the Office of Medicines Safety Monitoring (OMSM) of the TGA. Members of ADRAC are: Professor Duncan Topliss (Chair), Dr Michael Gold, Dr Vicki Kotsirilos, Associate Professor Cecilie Lander, Professor John McNeil, Associate Professor Peter Pillans, Associate Professor Simone Strasser, Dr Dana Wainwright

AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

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Please report **all** suspected reactions to these **Drugs of Current Interest**

Duloxetine (Cymbalta)
Dabigatran (Pradaxa)
Paliperidone (Invega)
Pramipexole (Sifrol)
Ranibizumab (Lucentis)

Rivaroxaban (Xarelto)
Rosuvastatin (Crestor or Visacor)
Sitagliptin (Januvia)
Strontium ranelate (Protos)
Varenicline (Champix)

1. Serotonin syndrome with duloxetine

Duloxetine is a serotonin and noradrenaline reuptake inhibitor recently approved for the treatment of major depressive disorder. It was included on the PBS in June 2008; to May 2009, over 200,000 prescriptions have been dispensed. Over this same period, 108 reports of suspected adverse drug reactions with duloxetine have been received. The commonly reported reactions include dizziness (10 cases), suicidal ideation (10), tremor (8), agitation (8) and serotonin syndrome (7).

Serotonin syndrome is caused by the accumulation of serotonin in the central nervous system. It is characterized by a triad of autonomic dysfunction, cognitive-behavioural changes and neuromuscular dysfunction. In five of the seven cases of reported serotonin syndrome, there was no evidence of other risk factors normally associated with this condition, such as concomitant use of other serotonergic agents or excessive dosing.

One of our reports describes a 40 year old female who developed serotonin syndrome after one dose

of duloxetine. She was admitted to hospital and a MRI scan showed no abnormalities. In the opinion of the treating physician, the events were causally related to duloxetine therapy.

A case report published recently describes a 70 year old female who developed serotonin syndrome within 48 hours of commencing the drug.¹ Symptoms rapidly resolved when duloxetine was ceased and re-emerged when duloxetine was re-introduced.

Based on this early post-market information, it appears that serotonin syndrome can occur with duloxetine treatment alone, even at therapeutic doses, as well as in combination with other drugs known to cause this syndrome. The Cymbalta Product Information has recently been updated to reflect this new information.²

References:

1. Hadikusumo B, Ng B. Serotonin syndrome induced by duloxetine. *Aust NZ J Psychiatry* 2009; 43: 581-582.
2. Cymbalta (duloxetine) Product Information. Eli Lilly Australia Pty Ltd.

2. Fixed Drug Eruption

A 68 year-old woman presented with a 12 month history of erosive painful vulvovaginitis, non-specific on biopsy and unresponsive to treatment. On examination she had severe ulceration of the introitus and vagina. Her medications, unchanged for several years, were atorvastatin, candesartan and venlafaxine. Atorvastatin was stopped and no other changes were made. Within two weeks all symptoms had resolved and four weeks after stopping the drug genital examination was normal

This case demonstrates an uncommon but important adverse event of Fixed Drug Eruption (FDE). Classically, FDE presents as a recurrent eruption occurring at the same site each time the drug responsible is taken. The lesion may be vesicular or bullous, appears within minutes to days of use and is often preceded by itching or burning.

The genital area is a well-recognised site for FDE in both males and females.^{1,2} Other areas such as previous skin trauma or inflammation may

sometimes be involved and some medicines are associated with a FDE that occurs preferentially at one site, for example oxycam-induced lip lesions.³

The most commonly implicated drug groups are antibiotics, analgesics and antihistamines, although FDE can occur with any medicine.

FDE may be acute, recurrent or chronic, with rapid resolution of the lesions on cessation of the causative drug. FDE should be considered a possible cause of an otherwise unexplained recurrent bullous or vesicular skin rash, especially in ulcerative genital conditions unresponsive to standard management.

References:

1. Sehgal VH, Gangwani OP. Genital fixed drug eruptions *Genitourin Med* 1986; 62: 56-58.
2. Fischer G. Vulvar fixed drug eruption, a report of 13 cases. *J Reproduct Med* 2007; 25: 81-85.
3. E.Özkaya-Bayazit. Specific site involvement in fixed drug eruption. *J Am Acad Dermatol* 2003; 49: 1003-1007.

3. Is it leflunomide lung?

ADRAC continues to receive reports of severe pulmonary disease, including interstitial lung disease (ILD) in association with leflunomide. In some cases, the association with leflunomide was not recognised early enough and resulted in a fatal outcome.

Reports of ILD with leflunomide alone or in combination with methotrexate (also unilaterally associated with ILD) were described in two previous Bulletins.^{1,2} In Dec 2006, 142 of the 699 reports with leflunomide described respiratory symptoms including 22 of ILD. In June 2009, the number of leflunomide reports has increased to 845, 196 of which describe respiratory symptoms including 39 of ILD. Of the 196 reports describing respiratory symptoms, 153 (78%) described concomitant use of methotrexate; 23 of the 39 ILD reports involved this combination.

Although clinically variable, manifestations of drug-induced pulmonary toxicity commonly include fever, cough (especially dry and non-productive), dyspnoea, pleurisy, chest pain, hypoxaemia and/or radiological evidence of pulmonary infiltrates (usually diffuse and/or alveolar).

New onset or worsening pulmonary symptoms with or without associated fever in those taking leflunomide with or without methotrexate may indicate development of leflunomide lung and should prompt further investigation.

4. Isotretinoin and acquired hearing impairment

Isotretinoin is a retinoid therapy indicated for the treatment of severe cystic acne unresponsive to conventional treatments. It is subsidised on the PBS and on average 150,000 items are dispensed through the PBS each year.

Isotretinoin therapy has been associated with acquired hearing impairment in previously well individuals, although the mechanism/s have not been established. This should not be confused with congenital hearing impairment, which is a known potential complication following fetal exposure to isotretinoin *in-utero*.

We have received 609 adverse event reports for isotretinoin dating back to 1982. These include 2 cases of unilateral hearing loss, 1 case of hearing loss at low frequencies and 2 cases of tinnitus.

If ILD develops, discontinuation of these therapies and implementation of a washout with cholestyramine (as recommended in the leflunomide Product Information) may be appropriate.³

In addition to ILD, leflunomide and methotrexate are both associated with a number of other severe, potentially fatal adverse effects, including liver failure, Stevens-Johnson syndrome and agranulocytosis. It is expected that the risks for ILD and other severe toxicities would be at the least additive when these drugs are used concomitantly.

Patients taking leflunomide, methotrexate or a combination of these should be monitored closely and informed about the possible early warning signs of toxicity, including ILD. They should be given Consumer Medicine Information for the prescribed drugs and advised to remain vigilant for signs that suggest a possible adverse reaction/s. Patients should contact their physician as soon as possible if these symptoms appear or worsen during therapy.

References:

1. Leflunomide: serious hepatic, blood, skin and respiratory reactions *Aust Adv Drug Reactions Bull* 2001; 20(2).
2. Leflunomide and interstitial lung disease. *Aust Adv Drug Reactions Bull* 2006; 25(6).
3. Arava, Arabloc (leflunomide) Product Information. Sanofi-Aventis Australia Pty Ltd.

Isotretinoin was the sole suspect in all 5 cases. The ages ranged from 14 to 46 years of age, and, where reported, duration of therapy ranged from 2 to 8 months. In all cases the outcomes were unknown.

Prescribers are reminded that isotretinoin has been associated with acquired hearing impairment. The hearing impairment can be unilateral or bilateral, and symptoms may include tinnitus, impaired hearing at certain frequencies and deafness. It is unknown whether hearing impairment is permanent. If isotretinoin-associated auditory toxicity is suspected, the drug should be ceased and the patient referred for audiology assessment.

WHAT TO REPORT? (you do not need to be certain, just suspicious!)

ADRAC encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, OTC medicines, herbal, traditional or alternative remedies. ADRAC particularly requests reports of:

- *ALL suspected reactions to **new drugs** (see **drugs of current interest**, front page)
- *ALL suspected drug interactions
- *Suspected reactions causing
 - Death
 - Admission to hospital or prolongation of hospitalisation
 - Increased investigations or treatment
 - Birth defects

For blue cards

Reports of suspected adverse drug reactions are best made by using a prepaid reporting form ("blue card") which is available from the website: <http://www.tga.gov.au/adr/bluecard.pdf> or from the Adverse Drug Reactions Unit ☎ 02-6232-8744.

Reports can also be submitted electronically, by going to the TGA website <http://www.tga.gov.au> and clicking on "report problems" on the left, by fax: 02-6232-8392, or email: ADR.Reports@tga.gov.au

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All correspondence to be addressed to: The Secretary, ADRAC, PO Box 100, Woden, ACT, 2606