

Prepared by the Adverse Drug Reactions Advisory Committee (ADRAC) and the Adverse Drug Reactions Unit (ADRU) of the TGA. Members of ADRAC are:
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AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

Volume 27, Number 1, February 2008

- ☆ MRI scans with gadolinium-containing contrast agents and the risk of NSF – caution in patients with renal impairment
 - ☆ Hepatic reactions with terbinafine
 - ☆ Interaction between glucosamine and warfarin
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Please report **all** suspected reactions to these **Drugs of Current Interest**

Atomoxetine (Strattera)
Ezetimibe and simvastatin (Vytorin)
Moxonidine (Physiotens)
Pregabalin (Lyrica)
Ranibizumab (Lucentis)

Rosuvastatin (Crestor or Viacor)
Strontium ranelate (Protos)
Varenicline (Champix)
Ziprasidone (Zeldox)

1. MRI scans with gadolinium-containing contrast agents and the risk of Nephrogenic Systemic Fibrosis – caution in patients with renal impairment

Nephrogenic systemic fibrosis (NSF) is a rare but potentially serious and life-threatening disorder involving fibrosis of the skin and connective tissues. To date, the cause has been unknown, but recently a strong association has been recognised between the development of NSF in those with serious renal impairment and the use of gadolinium-containing contrast agents used to enhance the quality of magnetic resonance imaging (MRI).^{1,2}

NSF usually presents as reddened or darkened patches, papules, or plaques, accompanied by swelling and thickening of the skin on extremities. Over a period of several days to weeks it may progress to contractures that impair joint movement. The disorder may affect systemic organs (liver, lungs, muscle and heart) leading to a fatal outcome.^{2,3} There is currently no known treatment for NSF, although improved renal function has been reported to alleviate the condition in some cases.

The TGA has received a single report of NSF in association with a gadolinium-containing contrast agent. The patient had pre-existing renal impairment and received gadodiamide for spinal MRI in 2002. Nine months later she presented with a one month history of skin thickening of the hands and feet, forearm pruritus and ulceration, dry eyes and mouth, reflux, and exertional dyspnoea. A diagnosis of NSF was not made until 2004 and her condition progressively worsened over the next 2 years and she became wheelchair-bound. This report was not submitted to the TGA until after it had been published in the literature in early 2007,⁴ which suggests the association may not be well recognised.

Several gadolinium-containing contrast agents are available in Australia and it appears that the incidence of NSF may vary between these agents. Gadodiamide (Omniscan), dimeglumine gadopentetate (Magnevist) and gadoversetamide (OptiMARK) have recently been contraindicated in patients with acute or chronic severe renal failure (glomerular filtration rate < 30 mL/min/1.73 m²); and the *Precautions* section of

product information documents for all agents has been updated.

The risk, if any, for developing NSF among patients with mild to moderate impairment of renal function is unknown at this time. In these patients, consideration should be given to the potential benefit from an examination involving gadolinium based contrast agents and the theoretical risk of NSF.

Australian Guidelines on the use of gadolinium-containing contrast agents in renal impairment are currently being developed (refer to <www.kidney.org.au>, <www.ranzcr.edu.au> and <www.nephrology.edu.au>). Doctors referring patients for contrast MRI should:

- ensure there is a sound indication for the procedure;
- screen all patients for renal dysfunction by obtaining a history and measuring renal function (serum creatinine/eGFR);
- establish the possibility of pregnancy (since the fetus is considered at high risk for NSF).

If renal function is found to be impaired or the patient is pregnant, this should be drawn to the attention of the radiologist.

Patients presenting with symptoms resembling NSF should be asked whether they have had MRI scans involving contrast media. Radiologists should include details of all contrast agents used when reporting scan results.

References:

1. Nephrogenic fibrosing dermopathy associated with exposure to gadolinium-containing contrast agents - St. Louis, Missouri, 2002-2006. *MMWR Weekly* 2007; 56: 137-141.
2. Richmond H, Zwerner J, Kim Y, Fiorentino D. Nephrogenic systemic fibrosis. Relationship to gadolinium and response to photophoresis. *Arch Dermatol* 2007; 143: 1025-1030.
3. Cowper S. Nephrogenic fibrosing dermopathy: the first 6 years. *Curr Opin Rheumatol* 2003; 15: 785-790
4. Cheung P and Dorai Raj A. Nephrogenic fibrosing dermopathy: a new clinical entity mimicking scleroderma *Int Med J* 2007; 37: 139-141.

2. Hepatic reactions with terbinafine

Oral terbinafine (Lamisil) is approved for the treatment of fungal infections of the nails and skin (ringworm) that are not responsive to topical therapy. ADRAC is concerned that in some cases the oral form of terbinafine may be selected without any trial of topical therapy, thereby putting the patient at risk of rare but serious and life-threatening toxicities such as agranulocytosis and other blood dyscrasias, Stevens-Johnson syndrome, and liver failure.

ADRAC has previously drawn attention to serious adverse reactions associated with orally administered terbinafine.^{1,2,3} Recently, the Committee reviewed a report describing an 81 year old female with previously normal liver function who developed cholestatic hepatitis some 3 weeks after commencing oral terbinafine treatment 250 mg daily for a fungal infection of the big toe. The patient subsequently died in hepatorenal failure.

Of the total 722 adverse event reports received up to January 2008 in connection with terbinafine (all dose forms), 70 describe hepatic reactions and most (61) implicated oral terbinafine as the sole suspected drug. Onychomycosis was the most

commonly cited reason for use of terbinafine; patient age ranged from 20 to 85 (median 58) years, and men and women were affected equally. Half of the reports documented onset of hepatic reaction within the first month and 80% within 7 weeks. Most of the reports document minor abnormalities of liver function but 3 describe fatal liver failure, 10 describe hepatitis, and 12 describe jaundice. Full recovery was noted in 27 reports but 34 cases had not recovered and the outcome remained unknown in 9.

ADRAC reminds prescribers that oral terbinafine can be associated with rare but serious and life-threatening toxicities. Doctors prescribing oral terbinafine should be confident there is a clear indication for its use. Oral terbinafine should be prescribed only after topical therapy has failed and for the shortest time possible, in accordance with the current Product Information.

References:

1. Life threatening blood dyscrasias with oral terbinafine. *Aust Adv Drug React Bull* 2006; 25(4): 15.
2. Terbinafine and blood dyscrasias. *Aust Adv Drug React Bull* 2004; 23(5): 19.
3. Terbinafine – a question of taste. *Aust Adv Drug React Bull* 1996; 15(1): 2-3.

3. Interaction between glucosamine and warfarin

The TGA has received 12 reports suggesting an interaction between warfarin and glucosamine. Most of the cases described changes in the international normalised ratio (INR) after patients previously stable on warfarin began taking glucosamine. In 2 cases, the INR fell slightly but in the other 10 cases the INR rose (peak INR, reported in 8 cases, ranged from 4.1 to 12). In most of the cases, the changes occurred from 4 to 20 days after commencing glucosamine and in one case, an INR rise occurred 2 days after the dose of glucosamine was increased. Most of the INR increases were asymptomatic but in one case a patient developed hyphaema and in another case the patient developed haemoptysis and petechiae.

The potentiating effect of glucosamine on warfarin activity has been highlighted in a report of 22 cases to the WHO Collaborating Centre for Drug Monitoring (which includes 9 of the Australian reports) and also by the UK's Medical and Healthcare products Regulatory Agency which described 7 cases of INR increases in patients commencing glucosamine when

previously stable on warfarin.^{1,2} The mechanism of this interaction is unknown. Product information documents for the warfarins note that “*there is some evidence that glucosamine might increase the activity of warfarin*” and that “*all patients taking warfarin should be specifically asked if they are taking complementary medicines of any kind.*”

Patients taking warfarin should be advised to consider the potential for interactions with other medicines, including complementary medicines and herbal remedies. ADRAC recommends patients taking warfarin should have their INR assessed within a few days and no later than two weeks after commencing or changing the dose of a complementary medicine.

References:

1. Yue Q-Y; Strandell J; Myrberg O. Concomitant use of glucosamine potentiates the effect of warfarin (abstract). *Drug Safety* 2006; 29: 911.
2. MHRA/CSM. Glucosamine adverse reactions and interactions. *Current Problems in Pharmacovigilance* 2006; 31: 8.

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 front of the "Schedule of Pharmaceutical Benefits" and the "Australian Medicines Handbook", or from the Adverse Drug Reactions Unit ☎ 02-6232-8744, or from the website:
<<http://www.tga.gov.au/adr/bluecard.pdf>>

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.

ISSN 0812-3837 © Commonwealth of Australia 2008

The Bulletin is also available on the Internet at: <<http://www.tga.gov.au/adr/aadrb.htm>>

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