Prepared by the Adverse Drug Reactions Advisory Committee (ADRAC) and the Adverse Drug Reactions Unit (ADRU) 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

Volume 27, Number 6, December 2008

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

Atomoxetine (Strattera)
Duloxetine (Cymbalta)
Ezetimibe and simvastatin (Vytorin)
Moxonidine (Physiotens)
Paliperidone (Invega)
Pramipexole (Sifrol)
Pregabalin (Lyrica)
Ranibizumab (Lucentis)
Rosuvastatin (Crestor or Viacor)
Sitagliptin (Januvia)
Strontium ranelate (Protos)
Varenicline (Champix)

1. Varenicline: the Australian experience so far

Varenicline (Champix) acts to relieve the cravings and withdrawal symptoms of smoking cessation and is used as an aid to stop smoking in adults. To minimise potential adverse reactions, treatment with varenicline is initiated in a gradually increasing dose titration schedule. Since January 2008 varenicline has been available on the Pharmaceutical Benefits Schedule but is restricted to individuals who have entered (or are about to enter) a comprehensive support and counselling program. To date, 210,000 PBS prescriptions for varenicline have been dispensed.

Overseas safety alerts have linked varenicline with the onset of serious neuropsychiatric side-effects, mainly behavioural changes, agitation and depression which may be accompanied by suicidal ideation.[1,2] The Australian Product Information alerts prescribers to the possibility of such effects with varenicline treatment.

To October 2008, we have received 339 adverse reaction reports with varenicline, 255 (72%) of which describe psychiatric symptoms including depression, aggression, agitation, abnormal dreams, insomnia, hallucination and anger. There have also been reports of suicidal/self-injurious ideation or behaviour.

While some patients may have experienced these types of symptoms as a result of nicotine withdrawal, it appears increasingly likely with accumulating experience that there is an association between varenicline and serious neuropsychiatric events.

Prescribers are reminded to advise patients of the types of neuropsychiatric symptoms that are outlined in the Champix Product Information and Consumer Medicine Information. Patients who develop these symptoms, including suicidal thoughts, while taking varenicline should seek urgent medical help and cessation of varenicline should be considered. Family and carers should be advised to be vigilant for any changes in behaviour, especially in smokers who have concomitant or previous psychiatric illness.

We have also received 15 reports of seizures in patients using varenicline. It is not known how many of these had a prior history or risk of a seizure disorder and there is no experience from clinical trials of varenicline in patients with epilepsy. Therefore prescribers are also advised to exercise caution when prescribing varenicline to patients with a history of seizure disorder.

References:
1. MHRA & CHM. *Drug Safety Update*, 2008; vol. 2/4.
2. www.fda.gov/cder/drug/infopage/varenicline/default.htm

2. Modafinil: adverse skin and psychiatric reactions

Modafinil (Modavigil) is a wakefulness promoting agent available in Australia since July 2002 for the treatment of patients with excessive daytime sleepiness associated with narcolepsy or chronic shift work sleep disorder; and as adjunctive treatment in obstructive sleep apnoea/hypopnoea syndrome. Modafinil is available on the Pharmaceutical Benefits Schedule as an authority-required medicine, for strictly-defined use in the treatment of patients with narcolepsy. To September 2008, 4,168 prescriptions have been issued for this medicine.

Recently, international attention has been drawn to the risk of serious adverse skin and psychiatric reactions with modafinil.[1,2] Since 2003 in Australia, we have received 10 reports with modafinil: 2 describe skin reactions, 5 describe serious psychiatric reactions and 3 describe gastrointestinal disturbance, rhinorrhoea and chest pain, respectively.

Skin Reactions

Non-specific skin rash may be the earliest presentation of Stevens Johnson syndrome, erythema multiforme or toxic epidermal necrolysis, all of which have been reported with modafinil overseas.[1,2] Serious, potentially life-threatening skin reactions to modafinil usually present within the first 5 weeks of treatment but isolated cases have occurred after 3 months.[2]

The two Australian reports describe the development of itchy face, eyes and skin and erythematous rash in a 48 year old female taking modafinil for 3 days; and urticarial rash in a 74 year old female taking the drug for 2 months. In both cases, the skin reactions resolved once the drug was ceased and recurred when it was re-introduced. In 1 case, re-challenge was at a much-reduced dose but the skin lesions were more severe, with ecchymotic lesions, considered vasculitic.

Psychiatric Reactions

Although modafinil-associated psychiatric reactions most commonly occur in those with a history of psychosis, depression or mania, they have also been reported in patients without a psychiatric history. The 5 Australian cases (2 males, 3 females) had a history of paranoid personality, depression, or post-natal depression. The presenting symptoms were anxiety, abnormal behaviour, guilt feelings, rapid relapse/onset of depression, suicidal ideation, suicidal behaviour, psychotic disorder and delusion. In 3 cases, the reaction occurred after only 1-3 doses but onset was > 1 year after the drug was commenced in the other 2 cases. All had recovered when the drug was ceased and positive re-challenge was reported in 1 case of depression. Overseas reports of psychiatric reactions have also described hallucinations, aggression and mania.

Prescribers should be cautious when prescribing modafinil to patients with a history of psychosis, depression or mania; alcohol, drug or illicit substance abuse are also reported risk factors.[2] At the first sign of rash, or if patients experience psychiatric symptoms, modafinil should be discontinued and not restarted.

References:
1. MHRA & CHM *Drug Safety Update*, 2008; vol. 1/8.
2. FDA *Drug Safety Newsletter*, Fall 2007; vol. 1/1.

3. Risks of fulminant liver failure when stopping drugs for the management of hepatitis B

Hepatitis B can be effectively controlled by drugs such as lamivudine (Zeffix), adefovir (Hepsera), entecavir (Baraclude), telbivudine (Sebivo) or tenofovir (Viread), but these do not cure the disease and often need to be continued indefinitely.

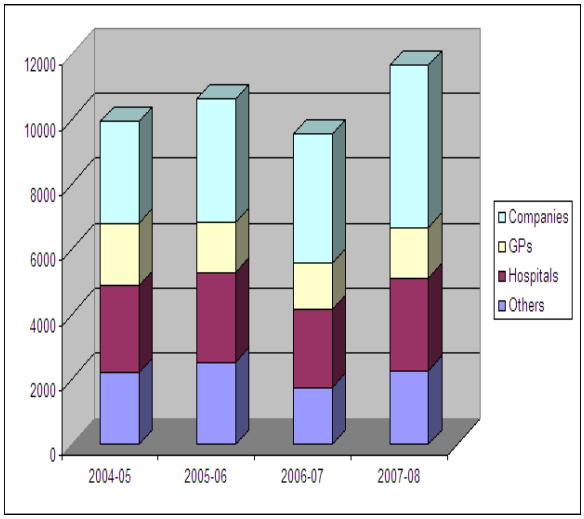
ADRAC is aware of at least 2 patients with previously well-managed hepatitis B who developed fulminant liver failure requiring a transplant when they decided to stop taking their medication without medical advice. While this rebound phenomenon is well known amongst health professionals, it may not be appreciated by patients who have the disease.

ADRAC requests that health professionals managing patients with hepatis B emphasise the importance of medication compliance. It is important to explain the risks associated with stopping the medications without first speaking with a doctor, and to ensure that patients have understood this advice.

4. Thank you for your reports

The number of adverse drug reaction reports received over the past 4 years has remained relatively constant at about 10,000 per year. While total numbers have been maintained, the relative number from GPs has declined from 19% of all reports in 2004/05 to 13% in 2007/08. Systems to facilitate reporting by GPs are under development. In the meantime, we encourage you to continue to use the methods available currently (see back page). Reporters should find the recently modified "Blue-card" much easier to complete and submit electronically than previous versions.

Our ability to monitor drug safety relies on your reports.



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

ISSN 0812-3837

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

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