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AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

VOLUME 20, NUMBER 2, JUNE 2001

- ☆ Update on bupropion (Zyban SR)
- ☆ Leflunomide: serious hepatic, blood, skin and respiratory reactions

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

Bupropion (Zyban)
Celecoxib (Celebrex)
Eprosartan (Teveten)
Leflunomide (Arava)
Mirtazapine (Avanza, Remeron)
Oseltamivir (Tamiflu)
Oxcarbazepine (Trileptal)
Quetiapine (Seroquel)
Raloxifene (Evista)
Repaglinide (NovoNorm)
Risedronate (Actonel)
Rivastigmine (Exelon)
Rofecoxib (Vioxx)
Rosiglitazone (Avandia)
Sildenafil (Viagra)
Tibolone (Livial)
Tramadol (Tramal)
Zolpidem (Stilnox)

1. UPDATE ON BUPROPION (ZYBAN SR)

(This article was posted on the TGA website on 14 May, 2001 at: http://www.health.gov.au/tga/docs/html/zyban.htm)

Bupropion (Zyban SR) was first marketed in Australia late in 2000 as a short-term aid to giving up smoking and has had very high usage. It was initially developed as an antidepressant. It is a selective inhibitor of the neuronal re-uptake of catecholamines in the brain but its mechanism to enhance the ability to quit smoking is unknown.

The assessment of reactions to bupropion use is difficult because many patients experience the effects of nicotine withdrawal in addition to the effects of bupropion. Since November 2000 the Adverse Drug Reactions Advisory Committee (ADRAC) has received 780 Australian reports of suspected adverse reactions in connection with the use of Zyban SR. In 758 of these, Zyban SR was implicated as the sole suspected drug. The more commonly reported problems involved **skin reactions** (307 reports), **psychiatric disturbances** (285), the **nervous system** (268), and the **gastrointestinal tract** (172) as indicated in Table 1 below.

Table 1: More Commonly Reported Reactions with Bupropion

Adverse Reaction	No of Reports
Skin	
Urticaria	167
Other rashes	86
Other itch	46
Neurological	
Dizziness/ataxia	78
Headache	68
Tremor	57
Convulsions/twitching	48
Paraesthesia/hypoaesthesia	40
Psychiatric	
Insomnia	78
Agitation	58
Anxiety	50
Depression	45
Gastrointestinal	
Nausea	87
Vomiting	30
Other	
Facial/angioedema	62
Chest pain	54
Shortness of breath	38
Increased sweating	33
Serum sickness	33

The profile of the drug is dominated by **hypersensitivity reactions** and **neurological and psychiatric effects**.

The majority of hypersensitivity reactions involve relatively minor skin reactions but there have also been reports of facial oedema or angioedema and serum sickness-like reactions. The latter describe a syndrome of a skin rash or urticaria with joint pain or swelling. The delayed onset ranging from 5 to 37 days (median: 17 days) after commencement of bupropion is also consistent with a serum sickness-like syndrome. In at least 16 of the cases, steroids were given.

Bupropion can cause seizures and is contraindicated in patients with epilepsy. It should be used with great caution in those with a predisposition to seizures including those abusing alcohol or taking another medication that can lower the seizure threshold. This includes most antidepressant and antipsychotic drugs, insulin, oral hypoglycaemic drugs and anorectic products.

Care also needs to be taken in prescribing bupropion for patients with a history of psychiatric conditions, and especially those taking drug therapy, because of the possibilities of interactions or additive effects. These are identified in the product information.

Recent media coverage has highlighted a small number of Australian reports to ADRAC of suspected adverse reactions to bupropion where the patient died. To date, there have been nine such reports in patients aged from 30 to 61 years of age. There has not been a single dominant mode of death.

The death of a patient may be caused by a drug or may be coincidental. Smokers are at increased risk of cardiovascular death and early symptoms of cardiovascular disease may have prompted therapy with bupropion. As with all reports with fatal outcomes, ADRAC seeks detailed follow-up information including post-mortem and coronial reports to aid its assessments of the individual cases.

ADRAC is satisfied, to date, that bupropion has not emerged as a cause of unexpected deaths. ADRAC meets every six to seven weeks and is keeping the drug's safety under close review.

2. LEFLUNOMIDE — SERIOUS HEPATIC, BLOOD, SKIN AND RESPIRATORY REACTIONS

Leflunomide (Arava) is an immuno-modulatory/immunosuppressant agent used for the treatment of active rheumatoid arthritis in adults. The drug has an active metabolite with a long half life (about 8 days) so recovery from adverse reactions may be prolonged. Since its marketing in Australia in early 2000, ADRAC has received 191 reports of suspected adverse drug reactions. Its registration was based on monotherapy but many of the reports received by ADRAC indicate that it is being used concomitantly with methotrexate (MTX). The profile of serious reactions reported includes liver dysfunction, haematological disorders, severe skin reactions and pulmonary dysfunction. Other less serious reactions which have been reported to ADRAC include other skin disorders, diarrhoea/abdominal pain, nausea/vomiting, weight loss, alopecia and angioedema or facial oedema (see Table 2).

Table 2: Adverse Reactions Reported to ADRAC for Leflunomide*

Reaction	Reports	Reports with MTX
Skin disorders (12 severe)	64	13
Diarrhoea/abdominal pain	63	16
Hepatic dysfunction	32	15
Nausea/vomiting	31	11
Haematological disorders	26	11
Weight loss	14	4
Alopecia	12	3
Angioedema or face oedema	10	2
Respiratory disorders	9	4

*more than one reaction may be recorded in one report

There have been 32 reports of **hepatic dysfunction**. Most (26) described elevated liver enzymes with minor symptoms or in the context of another organ dysfunction. There have been six severe cases with a fatal outcome in two patients. Fifteen of the 32 patients were taking concomitant methotrexate and only 9 of the 32 had recovered at the time the report was submitted.

Haematological reactions included pancytopenia (11), leucopenia/neutropenia (6), thrombocytopenia (3), anaemia (4) and thrombosis (2). One case each of anaemia and neutropenia and 4 cases of pancytopenia had a fatal outcome. Of the other 18 cases where the outcome was documented, 12 patients had recovered at the time the report was submitted. Seven cases of pancytopenia (including 3 fatalities), 2 cases of anaemia and 2 cases of white cell disorders involved the concomitant use of methotrexate.

Serious skin reactions consisted of cases of bullous eruption (4), skin ulceration (2), Stevens Johnson syndrome (2), vasculitis (2), erythema multiforme (1) and skin necrosis (1). Six of the 12 patients had recovered after leflunomide was stopped.

There have been 9 cases of **respiratory disorders**. Two reports described interstitial pneumonitis, one report described pulmonary infiltration and one described adult respiratory distress syndrome. Five other reports described dyspnoea. Methotrexate was used concomitantly in 4 cases.

Leflunomide has a profile of serious reactions including haematological, hepatic, skin and respiratory disorders. The concomitant administration of methotrexate may predispose patients to these effects. Prescribers should be aware of the possibility of these effects.

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

The Adverse Drug Reactions Advisory Committee (ADRAC) encourages the reporting of all **suspected** adverse reactions to drugs and other medicinal substances, including herbal, traditional or alternative remedies. The reporting of seemingly insignificant or common adverse reactions may highlight a widespread prescribing problem.

The Committee particularly requests reports of:

*ALL suspected reactions to NEW DRUGS, especially **DRUGS OF CURRENT INTEREST**

*ALL suspected drug interactions

*Reactions to other drugs which are suspected of significantly affecting a patient's management, including reactions suspected of causing

- •Death
- •Danger to life
- •Admission to hospital
- •Prolongation of hospitalisation
- •Absence from productive activity
- •Increased investigational or treatment costs
- •Birth defects

Reports of suspected adverse drug reactions are best made by using a prepaid reporting form ("blue card") which is available from the Adverse Drug Reactions Unit

☎ 02-62328386, 87, 88, or from the website: http://www.health.gov.au/tga/docs/html/adr.htm

Tear-out blue cards can also be found at the front of all recent editions of the "Schedule of Pharmaceutical Benefits", and at page 19 of the 2nd edition of the “Australian Medicines Handbook”.

Further information can be found from the medical and scientific staff in the ADRAC Secretariat:

Medical Officer: ☎ 02-62328381 Executive Secretary: ☎ 02-62328382

Fax: 02-62328392

(Problems with therapeutic devices should be reported on 1800-809361)

The Bulletin is also available on the Internet at:
http://www.health.gov.au/tga/docs/html/aadrbltn/aadrbidx.htm

ISSN 0812-3837

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