

From The Chief Medical Officer:
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HSS (MD)15/2001

To: All General Practitioners (for onward distribution to Practice Nurses & Practice Staff)
Community Pharmacists
Chief Executives of HSS Boards
Chief Executives of HSS Trusts
Directors of Public Health in HSS Boards)
Medical Directors of HSS Trusts) for onward distribution to
Directors of Pharmacy at HSS Boards) those involved in Smoking Cessation
Directors of Pharmacy at HSS Trusts) initiatives
Directors of Nursing in HSS Boards)
Directors of Nursing in HSS Trusts)
GP Advisers in HSS Boards
Prescribing Advisers in HSS Boards
Regional Medicines and Poisons Information Centre
Ulster Cancer Foundation
Chest, Heart and Stroke Association

31 May 2001

Dear Colleague

ZYBAN (AMFEBUTAMONE/BUPROPION HYDROCHLORIDE) – MODIFIED DOSAGE AND SAFETY PRECAUTIONS

The purpose of this letter is to notify you of new advice from Professor Breckenridge, Chairman of Committee on Safety of Medicines, on:

Modified dosage schedule for Zyban, a drug licensed as an aid to smoking cessation; and

New safety precautions for Zyban.

Attached to this letter are:

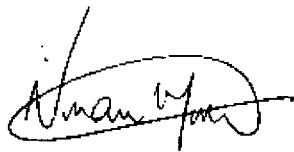
- a. the communication from Professor Breckenridge, Chairman of CSM;
- b. Zyban – important drug interactions; and
- c. Zyban – information for patients.

Please ensure that this important information is cascaded to all professionals involved in smoking cessation interventions.

Yours sincerely

Handwritten signature of Dr. Henrietta Campbell in black ink.

DR HENRIETTA CAMPBELL
Chief Medical Officer

Handwritten signature of Dr. Norman Morrow in black ink.

DR NORMAN MORROW
Chief Pharmaceutical Officer

MESSAGE FROM PROFESSOR A BRECKENRIDGE, CHAIRMAN OF COMMITTEE ON
SAFETY OF MEDICINES

30 May 2001

CEM/CMO/01/

Dear Colleague,

ZYBAN- MODIFIED DOSAGE AND SAFETY PRECAUTIONS

I am writing to advise you of a modified dosage schedule and new safety precautions for Zyban (bupropion /amfebutamone), a drug licensed as an aid to smoking cessation in nicotine addicted patients. Since its marketing at least 419,000 patients are estimated to have used Zyban. We have received over 5,000 Yellow Card reports, of which 126 were reports of seizures (in approximately 50% of these the patients had predisposing factors for seizure).

1. To minimise the risk of adverse effects, the Committee on Safety of Medicines has advised that, when starting Zyban the lower 150mg dose should be prescribed for the first six days, only increasing to 150mg twice daily on day 7 (The previous recommendation was to increase the dose on day 4).
2. Zyban is associated with a dose-related risk of seizures. There is also an increased risk of seizures occurring in the presence of factors which lower the seizure threshold.

To reduce the risk of seizures, prescribers are advised as follows:

- i) Zyban is contraindicated in patients
 - with a current seizure disorder or any history of seizures;
 - current or previous diagnosis of bulimia or anorexia nervosa;
 - with a known central nervous system (CNS) tumour;
 - experiencing abrupt withdrawal from alcohol or benzodiazepines.
- ii) Zyban must not be prescribed in patients with other risk factors for seizures unless there is compelling clinical justification for which the potential benefit of smoking cessation outweighs the increased risk of seizure. In such patients a lower dose of 150mg daily throughout the entire treatment period should be considered. Such risk factors include:
 - concomitant administration of any drug known to lower the seizure threshold (e.g. antipsychotics, antidepressants, antimalarials, theophylline, systemic steroids, tramadol, quinolones and sedating antihistamines)
 - alcohol abuse
 - history of head trauma
 - diabetes treated with hypoglycaemics or insulin
 - use of stimulants or anorectic products

Due to its complex pharmacology Zyban has considerable potential for interaction with other medicines. Therefore it is important to be aware of all medicines which patients are taking when considering their suitability for Zyban treatment. Please find attached information on important drugs which may interact with Zyban and an information sheet for patients. Further information on drugs which may interact with Zyban can be found in the Pharmaceutical Journal Vol 266 26 May 2001 No 7149 (www.pharmj.com).

Smoking is the single greatest cause of premature death in the UK, and is responsible for 120,000 deaths per year. Zyban is clearly effective as an aid to smoking cessation. Its safety will remain under close review - please report any suspected adverse reactions to Zyban via the Yellow Card Reporting Scheme to the Committee on Safety of Medicines/ Medicines Control Agency.

Should you require any further information, please telephone Dr Williams (020 7273 0369) at the Medicines Control Agency. [Message Ends]

**ZYBAN (AMFEBUTAMONE / BUPROPION HYDROCHLORIDE)
IMPORTANT DRUG INTERACTIONS**

Drug(s)	Effect of interaction	Suggested management
<p>Drugs that lower seizure threshold, e.g.: Antipsychotics* Antidepressants* Antimalarials Tramadol Theophylline Systemic steroids Sedating antihistamines, Quinolones</p> <p>Diabetic patients treated with hypoglycemics or insulin</p> <p>Stimulants /anorectic agents</p>	<p>Increased risk of seizure as Zyban is known to lower the seizure threshold.</p>	<p>Must not be administered concomitantly with Zyban unless there is a <i>compelling clinical justification</i> for which the potential medical benefits of smoking cessation outweighs the potential risk of seizure. In such patients a maximum dose of 150mg of Zyban is recommended throughout treatment.</p>
<p>Drugs metabolised by the CYP2D6 enzyme, e.g.:</p> <p>Beta-blockers e.g. metoprolol Type 1c antiarrhythmics e.g. flecainide, propafenone Captopril Loratadine Codeine/ dihydrocodeine /dextromethorphan</p> <p><i>*also metabolised by CYP2D6</i></p>	<p>Zyban inhibits the CYP2D6 and therefore there may be increased plasma levels of drugs metabolised by this enzyme.</p>	<p>If Zyban is added to the treatment regimen, the need to decrease the dose of the original drug should be considered, e.g. with narrow therapeutic indices, the expected benefit of treatment with Zyban should be carefully considered compared with the potential risks.</p> <p>In patients already on Zyban concomitant therapy should be initiated at the lower end of the dose range of the concomitant drug.</p>
<p>Drugs which may inhibit/affect the metabolism of Zyban e.g.:</p> <p>Cimetidine Sodium valproate Orphenadrine Cyclophosphamide Ifosfamide</p>	<p>Potential for increased plasma levels of Zyban and associated adverse effects.</p>	<p>Monitor for increase in adverse events associated with Zyban (e.g. dry mouth, insomnia) or the concomitant therapy. Reduce the dose if necessary.</p>
<p>Levodopa</p>	<p>Evidence of increased adverse effects</p>	<p>Monitor for increase in adverse events associated with Zyban (e.g. dry mouth, insomnia) or the concomitant therapy. Reduce the dose if necessary.</p>
<p>Monoamine oxidase inhibitors</p>	<p>Potentiated monoamine levels.</p>	<p>Contraindicated. >14 days should elapse between discontinuation of irreversible MAOIs and initiation of Zyban. For reversible MAOIs the period depends on the elimination half life of the product.</p>

ZYBAN - INFORMATION FOR PATIENTS

As with all medicines Zyban is associated with certain side effects, these have to be carefully weighed up against the known health benefits of stopping smoking. Zyban may not be suitable for all patients who wish to stop smoking. It is extremely important that you discuss with your doctor, who is familiar with your medical history, your suitability for Zyban treatment.

If you are going to start taking Zyban:

- Tell your doctor if you have ever had a fit or convulsion or unexplained blackout.
- Tell your doctor or pharmacist if you are taking any other medicines, either those prescribed by your doctor or those bought without a prescription.
- When starting Zyban one tablet to be taken once a day for the first 6 days of your treatment course, then one tablet twice a day for the rest of the treatment course. Do not take more than one tablet at any one time and not more than two tablets in a day.

If you are currently taking Zyban:

- If you have started Zyban on the original schedule, increasing the dose on day 4, and feel well, you should continue.
- There are certain medicines and medical conditions where it may be necessary that your dose of Zyban is reduced. Tell your doctor or pharmacist :

if you have any of the following medical conditions:

- If you have ever had a head injury
- If you have diabetes that needs to be treated with insulin or other medicines
- If you drink heavily

if you are taking any of the following medicines:

- Anti-malarial medicines (for example, chloroquine, proguanil)
- Certain antihistamines some of which may be used for sleep problems (for example, Piriton, Dimotane, Nytol or Panadol Night)
- Medicines to treat depression or medicines to treat other mental illness (for example clozapine, risperidone, thioridazine or olanzapine)
- Theophylline, which is a medicine used to treat chest conditions such as asthma
- Steroids taken as tablets or injections (for example, prednisolone)
- Certain antibiotics (for example, ofloxacin, levofloxacin or norfloxacin)
- Tramadol, which is a strong pain killer
- Slimming medicines or other stimulant medicines

- While you are taking Zyban it is very important to tell your doctor or pharmacist before you take any new medicines.

Please read the Zyban Patient Information Leaflet carefully.