



WHO COLLABORATING CENTRE  
FOR INTERNATIONAL  
DRUG MONITORING

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# **ADVERSE REACTION NEWSLETTER 1998:2**

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**NATIONAL DRUG MONITORING CENTRES -  
DRUG SAFETY ISSUES**

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This newsletter contains information reported to the WHO and WHO Collaborating Centre for International Drug Monitoring; however, the

information reported does not necessarily reflect the official views, decisions or policies of the World Health Organization.

## **NATIONALLY CIRCULATED INFORMATION**

### **Australia**

ADRAC Bulletin Vol 17, No 2, May 1998

#### ***Ticlopidine update***

Ticlopidine (Ticlid) is an inhibitor of platelet aggregation used in the prevention of stroke in patients with known vascular disease who are intolerant of or unresponsive to aspirin. It is also frequently used in association with the implantation of vascular stents. In the two year period to February 1998, ADRAC has received 110 reports of suspected adverse reactions in association with ticlopidine. Most (77) implicated ticlopidine as the sole suspected drug cause of the reaction. Ages ranged from 33 to 85 (median 67) years. For the 97 reports which provided the information, onset occurred within the first month in 72% of cases with only 3 reports documenting onset after three months. The major adverse reactions are white cell disorders, and haemorrhagic reactions which may be due to thrombocytopenia or platelet dysfunction. Agranulocytosis (19 reports) and neutropenia (17) comprised one third of the total reports on ticlopidine. These **white cell disorders** were sometimes accompanied by fever/rigors (7), pharyngitis (4), mouth ulcers (3), hepatitis (2), thrombocytopenia (3) or anaemia (2). Four of the reports of agranulocytosis were accompanied by bone marrow biopsy reports documenting maturation arrest of myeloid precursors consistent with a drug-induced aetiology. Of the 36 reports of white cell disorders, 22 patients had recovered and 14 had not recovered at the time the reports were submitted. There were no fatalities.

In addition to the three reports of **thrombocytopenia** with a white cell disorder, there were 7 other cases of thrombocytopenia. Three were accompanied by purpura including one case which involved a rectal haemorrhage. Another case had concomitant haematuria and haemolysis. There have also been overseas reports of thrombotic thrombocytopenic purpura in association with ticlopidine. There were four other reports of **haemorrhagic effects** not related to thrombocytopenia, consisting of one report each of haemorrhagic colitis, pulmonary haemorrhage (with cardiac failure, diffuse bleeding noted at bronchoscopy), purpura, and unspecified life threatening haemorrhage (with purpura).

Prescribers should be aware that ticlopidine may be associated with blood dyscrasias, particularly neutropenia or agranulocytosis which may be of sudden onset. The product information for ticlopidine warns that the period of maximum risk is from 3 weeks to 3 months after starting therapy. Patients should be advised to report promptly any occurrence of fever, chills, sore throat and/or mouth ulcers which may indicate neutropenia or agranulocytosis. Prolonged or unusual bleeding, bruising, purpura or dark stools may indicate thrombocytopenia or platelet dysfunction. If any of these occur ticlopidine should be withdrawn immediately.

#### ***Protease inhibitors***

The introduction of the protease inhibitors indinavir (Crixivan), ritonavir (Norvir), saquinavir (Invirase) and nelfinavir (Viracept) has been a significant advance in the treatment of patients with HIV/AIDS.

Health professionals who treat HIV/AIDS patients would be well aware of the spectrum of adverse effects of these agents. However, their effectiveness in combination with other antiviral agents has resulted in many patients being treated in the general community and it is important for all practitioners to be aware of some of their more unusual adverse effects. Three important adverse reactions of the protease inhibitors have emerged - lipodystrophy, hyperglycaemia and nephrolithiasis.

The most common effect is the development of **lipodystrophy**. This involves a peripheral lipodystrophy with mobilisation of the lipid stores in the face, arms and legs. ADRAC has received 94 reports of this syndrome. Most (92) have involved indinavir with 4 reports implicating ritonavir and 5 with saquinavir. In 4 reports, more than one protease inhibitor was being used. Almost all of the reports describe facial lipodystrophy usually characterised by facial thinning or hollow cheeks. There is usually visible wasting of the arms and legs with relative central obesity. Time to onset varied from 5 days to more than a year after commencement of therapy but most reports described an onset time of 6 months or more. There is no information on recovery at this stage. It has been estimated that this syndrome may affect about 60% of patients taking protease inhibitors.

The possibility that protease inhibitors could be associated with **new onset diabetes mellitus, hyperglycaemia, or exacerbation of existing diabetes mellitus** was first raised last year. ADRAC has received 6 reports of hyperglycaemia, 5 reports of the development

of diabetes and 3 reports of aggravation of diabetes in association with the protease inhibitors. Indinavir was a suspected drug in

11 of these reports and saquinavir was a suspected drug in the other three cases. Time to onset varied from one to 19 months, but usually a few months after protease inhibitor therapy commenced. Two of the 14 patients were reported as recovered after the drug was withdrawn, and of the others, 3 had been initiated with antidiabetic therapy, 3 had increased insulin requirements, 2 had made dietary modifications and the other 4 were being monitored.

**Nephrolithiasis** appears to be an effect of indinavir only. The product information for indinavir notes that signs and symptoms of nephrolithiasis including flank pain with or without haematuria have been reported in 3.6% of patients receiving the drug. Of the 204 reports received by ADRAC involving indinavir, 47 have described either kidney stones, haematuria, loin/flank/kidney pain or crystalluria. Time to onset has varied from the same day the drug was started to 19 months after commencement, although two thirds of the cases have occurred in the first 3 months of use. Adequate hydration is essential to help reduce the risk of this complication.

Reference:

Carr A, Samaras K, Burton S et al. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. *AIDS 1998; 12: 6927-34.*

Comment: The term Fat redistribution has recently been introduced in WHO-ART.

**Methotrexate**

In 1994, ADRAC described two patients who developed methotrexate toxicity, one with a fatal outcome, after using excessive doses of low-dose methotrexate for treatment of rheumatoid arthritis. In both of these cases, despite written instructions and verbal advice, the patients took their tablets daily instead of weekly. Recently, ADRAC received a report of another case of fatal aplastic anaemia in which an elderly female with rheumatoid arthritis took 7.5 mg of methotrexate daily instead of 7.5 mg weekly. ADRAC is now aware of 6 cases in which there is evidence that methotrexate was taken more frequently than once a week and three of these had a fatal outcome.

For all patients being treated with weekly methotrexate, great care should be taken to give and repeat clear instructions on dosage. In particular, prescribers should *WHO ADR Newsletter 1998:2, page 2*

**specify a particular day of the week**, preferably a day of some significance to the patient. For example, "Take two tablets each Tuesday".

Reference:

ADRAC. Low dose methotrexate - toxic if not taken correctly. *Med J Aust 1994; 161: 152.*

**Interaction between miconazole oral gel and warfarin**

Drug interactions with warfarin are of major importance. Imidazole and triazole antifungal agents such as fluconazole, ketoconazole, itraconazole and miconazole are known to inhibit cytochrome P450 enzymes and potentiate the anticoagulant effect of warfarin. The interaction between warfarin and miconazole oral gel has been reported in Australia and New Zealand, but the receipt of 3 reports by <sup>1,2</sup>ADRAC within the past 12 months indicates that its importance is perhaps not widely appreciated. One of these reports is described below.

An elderly female had been taking warfarin 2.5 mg daily for six years after an aortic valve replacement.

During this time her international normalised ratio (INR) had been stable within the range 2.5-3.5. She was prescribed miconazole oral gel (Daktarin) which she applied four times daily, for treatment of oral thrush. After six days miconazole was stopped and five days later she presented with bruising on the arms and legs and a petechial rash on the left leg. Her INR was found to be 15.6. She was treated with fresh frozen plasma and vitamin K and her INR returned to normal in three days. ADRAC has received 11 reports documenting an interaction between warfarin and miconazole oral gel. They described elevations in INR to between 7.5 and 15.6. In five cases, there were no symptoms and in the other six cases, the patients presented with bruising, haematuria, or mucocutaneous bleeding. It may be thought that as miconazole oral gel is a topically applied medication its absorption is limited. However, considerable absorption can occur through inflamed oral mucosa or from the bowel after swallowing the gel. Prescribers should counsel their patients taking long term warfarin about the possibilities of drug interactions and be aware that miconazole oral gel has this potential. Prescribers should also be aware that miconazole oral gel is available without prescription.

References:

1. Shenfield GM, Page M. Potentiation of warfarin action by miconazole oral gel. *Aust NZ J Med 1991; 21: 928.*

2. Pillans P, Woods DJ. Interaction between miconazole oral gel (Daktarin) and warfarin. *NZ Med J* 1996; 109: 346.

## Canada

Canadian Adverse Drug Reaction Newsletter, Vol 8, No 2, April 1998

### **Alendronate-induced esophagitis**

Alendronate sodium (Fosamax<sup>®</sup>), an amino-bisphosphonate, is an inhibitor of bone resorption approved for use in Canada for the treatment of Paget's disease and for the prevention and treatment of postmenopausal osteoporosis.

From December 1995, when Fosamax<sup>®</sup> was approved for sale in Canada, to January 1998 the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) received 138 reports, of which 78 were suspected gastrointestinal reactions associated with the drug. Thirteen reports described esophageal reactions: esophagitis (9), esophageal ulceration (3), esophageal stricture (1).

The current recommendations for alendronate administration given in the product monograph are intended to facilitate delivery to the stomach and thus reduce the potential for esophageal irritation:

- The tablet should be swallowed with a full glass of water (200–250 ml) at least 30 minutes before the first food of the day.
- The patient should remain upright for at least 30 minutes after taking the tablet *and* after the first food of the day.
- Worldwide, the labelling for Fosamax<sup>®</sup> has been revised: the contraindications have been expanded to include patients who have esophageal abnormalities that result in delayed emptying (e.g., stricture or achalasia) and those who are unable to stand or sit upright for at least 30 minutes.

### **Dorzolamide hydrochloride (Trusopt<sup>®</sup>)**

Dorzolamide, a topical carbonic anhydrase inhibitor, is used to treat elevated intraocular pressure. Since first marketed in December 1996, the CADRMP has received 24 reports of suspected ADRs associated with this drug. Of these, 17 reports described 25 adverse effects not consistent with the product information or labelling and involved 8 women, 3 men and 6 patients of unknown sex, aged between 60 and 92 years. The unexpected reactions classified by system organ class include:

- *Cardiovascular disorders*: arrhythmia and chest

pressure sensation (1 case); hypertension (2); aggravated hypertension (1); palpitation (1); noninflammatory swelling (1)

- *Gastrointestinal disorders*: severe heartburn (1)
- *Visual and hearing disorders and psychiatric disorders*: anxiety, disorientation, auditory and visual hallucination (1); blindness (2); corneal edema (1); foreign body sensation (2); uveitis and posterior synechiae (1)
- *Body as a whole*: epistaxis (1); nasal congestion (1)
- *Central and peripheral nervous system disorders*: epileptic absence and petit mal (1)
- *Skin disorders*: alopecia (1); urticaria (1)

### **Hydroxychloroquine sulfate (Plaquenil<sup>®</sup>)**

Hydroxychloroquine, indicated for suppressive treatment and treatment of acute attacks of malaria, is also indicated for the treatment of discoid and systemic lupus erythematosus and of rheumatoid arthritis in patients who have not responded satisfactorily to drugs with less potential for serious side effects. With the increased use of the drug in connective tissue diseases, recent concerns have arisen regarding hydroxychloroquine's retinal toxic effects.

In 1997 the CADRMP received a report involving a 7-year-old girl who had been treated for polyarthropathy for 3 or 4 years. In April 1997 she experienced retinopathy, scotoma, circular ring, macular dysfunction and macular toxic effects. At the time of reporting, 6 months later, the patient had not yet recovered.

### **Atorvastatin calcium (Lipitor<sup>™</sup>)**

Within 1 or 2 days after starting therapy with atorvastatin (10 mg/d) for elevated cholesterol levels, a 67-year-old man complained that he "did not feel right"; a rash developed shortly afterward. A week later he had shortness of breath and increased weakness. On admission to hospital 3 weeks after the start of atorvastatin therapy he had a petechial rash and ecchymosis. The hemoglobin level was 55 (normally 140–180) g/L, the platelet count 7 (normally 130–400)  $\times 10^9$ /L and the erythrocyte count 1.48 (normally 4.4–5.8)  $\times 10^{12}$ /L. The blood counts had been normal 4 months earlier. Bone marrow biopsy revealed aplastic anemia. The atorvastatin therapy was stopped; 6 days later the hemoglobin level was 109 g/L, the platelet count was 60  $\times 10^9$ /L, and the erythrocyte count was 3.35  $\times 10^{12}$ /L. The outcome of the patient was unknown at the time of reporting. Concomitant medications included levothyroxine, furosemide, nifedipine and metoprolol, all

of which he had taken for more than 5 years; lovastatin was taken for several years up until the start of the atorvastatin therapy.

### ***Risperidone (Risperdal™)- carbamazepine interaction***

A 17-year-old mentally challenged young woman experienced an increase in carbamazepine serum levels after the start of therapy with the antipsychotic drug risperidone (1 mg twice daily). She had been taking carbamazepine (1400 mg/d) for 5 years and had good seizure control. Her carbamazepine level 2 weeks before the start of the risperidone therapy was 49 (normal therapeutic range 16–50) F mol/L. One week after starting risperidone the patient was vomiting, had multiple seizures, was irritable and was lethargic between seizures. She was admitted to hospital 3 days later. Pneumonia was diagnosed, and a toxic carbamazepine level of 105 F mol/L was detected. The risperidone was stopped and the carbamazepine withheld. Four days later the patient's carbamazepine level was 26 F mol/L, and the carbamazepine therapy was restarted. The possibility of an overdose with carbamazepine was ruled out.

### ***Venlafaxine hydrochloride (Effexor®)***

Vasospastic (Prinzmetal's) angina developed in a 23-year-old man 8 days after the start of therapy with venlafaxine (37.5 mg twice daily) for depression. The patient had 2 episodes of central and crushing chest pain. The first, occurring 8 days after the start of treatment, woke him in the night and lasted about 45 minutes. The second occurred 2 days later in the early morning and lasted 9½ hours. An electrocardiogram (ECG) in the emergency department showed 1 mm elevation of the J junction in lead 2 and 3, and atrioventricular fibrillation with flattening of the ascent of the T wave in lead 3 only. A second ECG 4 hours later showed 0.5 mm elevation of the ST segment in lead 3, with very slight convexity of the ST segment of a flat T wave. The total creatine kinase (CK) level was 259 (normally 20–235) U/L, the CK MB (myocardial component) was 29 (normally 0–5) UG/L, and the CK MB relative index was 11 (normally 0–4), which is consistent with myocardial ischemic injury. On both occasions the pain subsided spontaneously. Nontransmural myocardial infarction of the inferior wall was diagnosed, and the patient was admitted to the cardiac care unit. On admission, an echocardiogram was normal. Angiography done the following day showed minor coronary artery disease in the right coronary artery, *WHO ADR Newsletter 1998:2, page 4*

and a left ventriculogram showed mild inferobasal hypokinesis. The venlafaxine therapy was stopped 3 days after admission. At the time of the report the patient was asymptomatic. He was considered to have virtually no risk factors for heart disease and exercised regularly.

### **Chile**

Boletín Informativo sobre Medicamentos Vol 14, No 3, December 1997

### ***Thrombocytopenia and neutropenia associated with diclofenac***

Diclofenac is a NSAID prescribed for the treatment of pain, inflammatory and rheumatic disorders. Most of the ADRs are related to gastrointestinal bleeding and kidney disorders less frequently with the hematopoietic system. Thrombocytopenia and neutropenia associated with this drug is not common.

There was only previously one report of thrombocytopenia related to patients exposed to diclofenac.

There are also two cases describing neutropenia with this drug, in one case a woman 63 years old and in the other one a man 72 years old. In case one rechallenge was performed

### **Denmark**

Ugeskrift for Læger, 13 April 1998

### ***Mefloquine - neuropsychiatric reactions are often serious and persistent***

The Danish Adverse reaction section in 1994 reported of two serious psychiatric reaction after therapeutic doses of mefloquine. Since then, another 7 cases have been reported. Five of the reactions appeared after prophylactic use of mefloquine, four of them after the first to third dose, but one only three months after starting prophylaxis.

The Danish cases show that these reactions are relatively common in prophylactic use, contrary to what is mentioned in product résumé, and that they can persist a long time after stopping the drug. In Great Britain a total of 185 neurological and 234 psychiatric reactions had been reported up to August 1996 after mefloquine use. 20% of these appeared only after more than 5 weeks' treatment.

In a study by Barret et al. the adverse reaction frequency in prophylaxis with mefloquine was compared with that

of proguanil+chloroquine. In the mefloquine group 27% had neuropsychiatric reaction, while the frequency in the other group was 16%.

References:

Barrett PJ et al. Comparison of adverse events associated with use of mefloquine and combination of chloroquine and proguanil as antimalarial prophylaxis: postal and telephone survey of travellers. *Br Med J* 1996; 313: 525-8

## Finland

Tabu, Vo I 6, No 2, 1998

### ***St John's wort - an antidepressant***

In short term studies St John's wort extract has been shown to have few and minor adverse effects. In an open four-week follow-up study, 3,250 patients used St John's wort extract (hypericin content of 1.08 mg per day) for the treatment of depression, anxiety and sleep disorders. Of all these patients, 2.4 per cent reported adverse effects and 1.5 per cent discontinued the treatment. The most commonly reported adverse reactions were gastrointestinal symptoms, skin reactions and asthenia. In this study laboratory tests were not made regularly.

Hypericin in St John's wort extract causes photosensitivity when administered in large doses. Tests in animals have proved that this adverse reaction is dose dependent, and it has been concluded that in humans the symptoms of phototoxicity would result from a dose 30 times the therapeutic dose. In the mentioned studies phototoxicity was not reported.

Fifty volunteers were administered 600 mg x 3 (equivalent to 5.4 mg/day of hypericin) St John's wort extract, and subjected to UVA light radiation for fifteen days. It was found that subjects with sensitive skin became sensitive to UVA light. The hypericin content in the subjects' blood plasma was twice as high as that of a patient being treated for depression with the recommended dosage of St John's wort extract. Synthetic hypericin, administered intravenously to AIDS patients, caused photosensitivity at a dose equivalent to 35 times the therapeutic dose used in treatment of depression.

As yet, there are no research reports on the adverse reactions following long term use of St John's wort extract, nor on its potential interactions with other drugs. The use of St John's wort extract during pregnancy or lactation is not advised, as there is insufficient information of its safety

## France

Report from the French Pharmacovigilance Commission Meeting. December 11<sup>th</sup> 1997

### ***Assessment of the hepatic adverse effects of Euphytose***

(Crataegus; passion flower; guarana; kola; valerian; ballota).

Euphytose is a phytotherapeutic product used for sedative and antispasmodic purposes. It has been available on the market as tablets and oral solution since 1957.

23 cases of gastrointestinal and hepatic effects have been reported in patients exposed to this product.

3 out of 18 reports of hepatic effects were classified as possible; with fulminant hepatitis needed a hepatic transplantation. A 13,5 year old girl; another case with high SGTP and bilirubinemia associated with gastrointestinal disturbances but with a favorable outcome in a 35 year old man; another case of cholestasis associated to cytolysis in a 40 year old woman (Euphytose was used in a dosage higher than the daily dose recommended in the SPC).

Of the 5 reports of GI effects (nausea, abdominal pain, diarrhoea) 2 were classified as possible and 1 as possible. Taking in account the number of cases reported, some of them in children and with high doses, the National Pharmacovigilance Commission has proposed to include in the SPC, an additional statement concerning the side effects as follows:

"Rare cases of hepatic disorders have been reported, in patients during the treatment with this product, specially in children and in cases of over-dose.

GI adverse effects are also rarely reported".

## Germany

Deutsches Ärzteblatt 95, No 11, p. A-627, 1998

### ***Capillary Leak Syndrome in monoclonal gammopathy (kappa light chains) following subcutaneous interferon beta-1b***

There is a possible link between the subcutaneous administration of interferon beta-1b and the development of fatal Capillary Leak Syndrome.

This was found by the observation of a single case of a female patient who was treated with 8 MIU Betaferon for symptoms of encephalomyelitis disseminata (probable multiple sclerosis), went into shock and died with signs of multiple organ failure within less than 48 hours. It is

possible that this therapy triggered intensive autoimmune reactions on top of a previously existent intensive b-cell activation, as indicated by findings of monoclonal gammopathy and hypergammaglobulinaemia. Severe agnogenic perimyocarditis, which was observed prior to the patient MS, could also be viewed in this context.

The assessment of this observation is based on the mode of action of interferon beta-1b which, in the sense of immunomodulation, suppresses the TH1-mediated cytotoxic immune reaction by releasing interleukin-10.

The manufacturer of betaferon has already announced the inclusion of a warning in its product information.

### ***Current status of the risk/benefit assessment of calcium antagonists***

The Executive Committee of the Drug Commission and its expert members have dealt in detail with this subject and relevant studies, particularly those from the last two years, and have come to the following conclusion:

1- At this time, it cannot be confirmed that the risk/benefit ratio is unfavourable for rapid-acting calcium antagonists in rapid-release presentation for the treatment of stable angina pectoris and arterial hypertension. However, the possibility can also not be ruled out.

2- They should no longer be used in the treatment of stable angina pectoris or arterial hypertension.

3- In the case of long-acting calcium antagonists, a favourable prognostic effect for the registered indications cannot currently be considered proven beyond doubt. Therefore, long-acting calcium antagonists should also not be used if the aim of therapy is not only to improve the symptoms, but also to reduce morbidity and mortality.

4- If therapy with the aim of improving the prognosis as regards morbidity and mortality is not possible due to contraindications or intolerability, calcium antagonists with sustained-release effect can be used.

5- Rapid-acting calcium antagonists in rapid-release form should only be used for the acute treatment of specific indications under consideration of the risk and under close medical observation.

No statements can be made at this time as regards an elevated risk of haemorrhage and cancer.

## **Ireland**

Irish Medicines Board Drug Safety Newsletter. No 7, March 1998

### ***Carbaryl-containing products***

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Following assessment of the available data IMB is currently revising the recommendations for use of carbaryl-containing products with the companies concerned. The revised changes are summarised as follows:

1- Carbaryl-containing products should only be used for treatment of live lice infestation and not for prevention.  
2- Continued prolonged treatment with carbaryl-containing products should be avoided. They should not be used more than once a week and for no longer than three consecutive weeks.

It is important to remember that over time lice may become resistant to the insecticides used in their treatment. It is therefore advisable that hospitals and Health Boards recommend rotation of the products used approximately every three years.

### ***Anexate & Anectine***

The IMB has received several anecdotal reports of inadvertent use of one or other of the above parenteral products because of confusion arising with their respective product names. The potential for hazard should one of these products be used in place of the other is clearly significant.

Health professionals are reminded to exercise care when verbally requesting or writing either product name. It may also be helpful to use the non-proprietary names in order to prevent further cases of confusion and thereby avoid potential disasters.

Anectine - Suxamethonium

Anexate - Flumazenil

### ***Meloxicam (Mobic)***

Meloxicam is a NSAID indicated for short-term symptomatic treatment of acute exacerbations of osteoarthritis and in the long term symptomatic treatment of rheumatoid arthritis and the symptomatic treatment of ankylosing spondylitis.

Analysis of world-wide post-marketing surveillance data has shown that in common with other NSAIDs, serious and sometimes fatal gastrointestinal adverse reactions, including gastrointestinal haemorrhage, peptic ulcer and perforation, have occurred in association with meloxicam treatment. In some cases these reactions have occurred in patients known to be at risk of serious gastrointestinal reaction (e.g. past history of gastrointestinal disorders).

Meloxicam was authorised for use in Ireland in 1996 and since then the IMB has received 13 suspected adverse reaction reports associated with its use. Of these, eight involved gastrointestinal disorders namely anorexia,

dyspepsia, nausea, diarrhoea, haematemesis, perforated gastric ulcer and melaena. One of these cases resulted in a fatal outcome.

**Phentermine (Ionamin)**

Ionamin is the only anorectic agent available for use in Ireland and prescribers are reminded of the following restrictions to its use:

**Therapeutic indications:** Adjunctive therapy to diet, in patients with obesity and a body mass index (BMI) of 30 kg/m<sup>2</sup> or higher who have not responded to an appropriate weight-reducing regimen alone.

**Posology and method of administration:** It is recommended that treatment should be monitored under the care of physicians experienced in the treatment of obesity.

**Duration of treatment:** The duration of treatment is 4-6 weeks and should not exceed three months.

**Contraindications:**

1. Pulmonary artery hypertension
2. Severe arterial hypertension
3. Current or past medical history of cardiovascular disease or cerebrovascular disease
4. Propensity towards drug abuse, known alcoholism
5. Children below 12 years

**Special precautions for use:** Cases of severe, often fatal, pulmonary artery hypertension, have been reported in patients who have received anorectic of the type in this product. An epidemiological study has shown that anorectic intake is a risk factor involved in the development of pulmonary artery hypertension and that the use of anorectics is strongly associated with an increased risk for this adverse drug reaction.

**Undesirable effects:** Cases of pulmonary artery hypertension have been reported in patients treated with this agent.

**New Zealand**

Prescriber update, No 16, April 1998

**Dependence with zopiclone**

Dependence and withdrawal effects with zopiclone do occur, although rarely. These effects can occur in people without prior substance dependence and who are taking the recommended dose. The duration of the treatment with zopiclone should be limited to < 4 weeks. Dose tapering on withdrawal may be necessary if treatment is continued for a long period.

The New Zealand Centre for Adverse Reactions Monitoring (CARM) has received 3 reports of dependence or withdrawal problems with zopiclone. One patient had been taking zopiclone 15 mg daily for 2.5 years. On missing one dose the patient became depressed and irritable and claimed to have a "fuzzy head". Another patient had taken zopiclone 7.5 mg every night for 6 months. With abrupt withdrawal the patient felt "strange in the head" for 2-3 days, but experienced no physical effects. The third person, who was also on lithium carbonate and thyroxine, was taking 11 tablets per day of zopiclone (82.5 mg) and experienced withdrawal phenomena (not described) with discontinuation.

**Adverse reactions of current concern**

A list of adverse reactions of current concern was first initiated in December 1994.

There are two reasons for this list.

- A- To raise the level of awareness of these adverse reactions.
- B- To evoke reports so that more information may be gathered and appropriate action taken.

The list is as follows:

Medicine	Adverse Reaction	Prescriber update reference
Alendronate	oesophagitis	No. 16, April 1998
Colchicine	serious toxicity	No. 16, April 1998
Herbal medicines	All adv. reactions	No. 13, Oct. 1996
Hormone replacement therapy	Venous thromboembolism	No. 16, April 1998
NSAIDs	renal damage	No. 16, April 1998 & No. 13, Oct. 1996
Mefloquine	Neuropsychiatric reactions	No. 15, Aug. 1997
Non-sedative antihistamines	cardiac effects	No. 7, Dec. 1994 & No. 15, Aug. 1997
Oral contraceptives	venous thromboembolism	No. 11, Feb. 1996

**Hypotonic-hyporesponsive episodes to immunisation**

Hypotonic-hyporesponsive episodes (HHE) are recognised serious reactions to immunisation, especially pertussis-containing vaccine.

Management involves checking the airway, breathing and circulation, then hospitalisation as a precaution. In reported cases, full recovery has occurred and there has been no long term sequelae. The paediatrician who

assesses the child should also advise on the completion of the immunisation programme.

### **Top ten adverse events to sumatriptan in the IMMP**

Sumatriptan (Imigran), a medicine used in the acute treatment of migraine and cluster headache, has been monitored in the IMMP since marketing began in April 1991.

Adverse reactions to sumatriptan are common, but usually minor and transient, and many patients find them acceptable because of the rapid relief they get from their migraine. In order to avoid alarm it is wise to inform patients prescribed sumatriptan for the first time unusual symptoms may occur. Practitioners should be aware that sumatriptan is contraindicated in the presence of ischaemic heart disease and Prinzmetal's angina, and that it should not be co-prescribed with ergotamine preparations.

### **The 10 most frequently reported adverse events to sumatriptan**

Number of patients (rate/1000 patients)

Adverse event	Injections (N=7875)	Tablets (N=3990)	Rate Ratio Injection/tablet
Sensory disturbance	295 (37.5)	48 (12.0)	3.1
Nausea/vomiting	203 (25.8)	96 (24.1)	1.1
Headache complications	198 (25.1)	42 (10.5)	2.4
Fatigue/malaise/somnolence	185 (23.5)	77 (19.3)	1.2
Chest pain	178 (22.6)	36 (9.0)	2.5
Injection site reaction	139 (17.7)		
Cardiac dysrhythmia	88 (11.2)	19 (4.8)	2.3
Dizziness/syncope	121 (15.4)	28 (7.0)	2.2
Throat tightness	72 (9.1)	7 (1.8)	5.1
Hot & cold feelings/shivering/sweating	71 (9.0)	16 (4.0)	2.3

## **Sweden**

News from Medical Products Agency, May 1998

### **Suspected connection between Roaccutane® and psychiatric problems**

Roaccutane can in Sweden be used only on prescription by specialists. FDA, USA recently informed about the risk of depression and suicidal thoughts with Roaccutane, and that stopping the drug may not be adequate measure. The mechanism for the reaction is not known.

The MPA comments that there may be several factors behind the reaction. Some of the patients developed depression only after end of treatment, and some of the patients had previously had depression. There are however, reports of some cases where depression decreased after stopping the drug and came back when restarting treatment.

The MPA has a total of 12 reports of psychiatric reactions with Roaccutane, whereof 9 with a causal relationship. No fatalities have been reported. The MPA has started a study of a cohort of 5 800 patients who were treated with Roaccutane some time between 1981 and 1990 to find out if there is a real increased risk of depression among these patients.

## **Tanzania**

Drug Information Bulletin Vol 9, No 2, 1997

### **Pharmacists asked to report adverse drug reactions**

The 10<sup>th</sup> Scientific Conference was organized by the Pharmaceutical Society of Tanzania. Tanzania Drug and Toxicological Information Service (SADATIS) prepared a presentation which aimed at raising awareness of adverse drug reactions to pharmacists working in either public or private sector on understanding of the programme of monitoring adverse drug reactions and to seek their cooperation on data collection and signal generation. The presentation also aimed at raising awareness of drug safety issues among pharmacists and other health care professionals.

Tanzania is a member country in WHO International Drug Monitoring programme since 1993. The underreporting problem is still facing the national centre as health care professionals do not have the culture for notification.

Staff at TADATIS have planned to make such presentations in various medical scientific and

pharmaceutical meetings. The overall objective will be to sensitise and stimulate healthcare professional in ADR reporting.

## United Kingdom

Current Problems in Pharmacovigilance Vol 24, March 1998

### ***Vigabatrin (Sabril) and visual field defects***

Vigabatrin (Sabril) is an anti-epileptic drug indicated for the treatment of epilepsy not satisfactorily controlled by other drugs. It is indicated as monotherapy only for infantile spasms (West's Syndrome). Adverse reactions to vigabatrin are predominantly neurological or psychiatric. In common with other anti-epileptic drugs, diplopia is a well-known side effect but other visual complaints are less well characterised.

In 1997, 3 cases of severe, symptomatic, persistent visual field constriction associated with vigabatrin treatment were described<sup>1</sup>. In all 3 cases constriction of the visual field was detected 2 to 3 years after the start of vigabatrin therapy.

Since December 1989, we have received a total of 41 UK reports of visual field defects (including 3 reports of tunnel vision). About 80,000 prescriptions for vigabatrin are dispensed annually in the UK.

A Prescription Event Monitoring (PEM) study, conducted by the Drug Safety Research Unit in Southampton, identified 4 cases of visual field defect in a cohort of 10,178 patients treated with vigabatrin. A further 7 cases were reported after the initial 6 month observation period. No similar cases of visual field defect were identified in the 61 other drug cohorts studied by PEM<sup>2</sup>. Although this issue is still under investigation, the current evidence suggests that the onset of visual field defects varies from one month to several years after starting vigabatrin. In most cases visual field defects persisted despite discontinuation of treatment.

Product information advises that visual field testing should be performed before treatment and during routine follow-up for patients on vigabatrin. Patients should be warned to report any new visual symptoms that develop after starting treatment with vigabatrin. Those with symptoms suggestive of possible visual field loss, should be referred for an urgent ophthalmological opinion. It may also be necessary to give careful consideration as to whether vigabatrin should be withdrawn.

## Reference

1. Eke T, et al. BMJ 1997; 324:180-181.
2. Stephen MDB, et al. Pharmacoepidemiology and Drug Safety 1997; 6 (S2): S18.

## Withdrawals

### USA

FDA MedWatch News, June 8, 1998

#### ***Withdrawal of Posicor***

Roche Laboratories announces the immediate voluntary market withdrawal of the antihypertensive and anti-anginal medication, Posicor (mibefradil dihydrochloride). The action is based on evolving information concerning the potential for drug interactions, some of them serious, that may occur when Posicor is taken together with some other medications.