



WHO COLLABORATING CENTRE  
FOR INTERNATIONAL  
DRUG MONITORING

Stora Torget 3  
S-753 20 UPPSALA  
Sweden

June 1999

---

---

# **ADVERSE REACTION NEWSLETTER 1999:2**

---

---

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

---

---

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 18, No 2, June 1999

### **Depression with inteferon**

Interferon alfa (2a-Roferon-A and 2b-Intron A) is used in a variety of conditions including leukaemias, some carcinomas, multiple myeloma, non-Hodgkin's lymphoma, malignant melanoma and more recently, hepatitis B and C. The most commonly reported adverse reactions in association with interferon alfa are flu-like symptoms such as fever, fatigue, myalgia, joint pain, and headache. Serious effects documented include severe hypersensitivity reactions, and haematological, hepatic, cardiovascular and neurological effects, particularly at high dose. Psychiatric effects have been described and include depression and suicidal ideation.

ADRAC has received 19 reports of depression or suicidal ideation associated with interferon alfa therapy. Eleven patients had depression alone, four had depression and suicidal ideation or attempt and there were four additional reports of suicidal attempts. Three of the reports of suicidal attempt were fatal.

#### Reference

1. Renault PF, Hoofnagle JH, Park Y et al. Psychiatric complications of long-term interferon alfa therapy. Arch Intm Med 1987; 147: 1577-80.

### **Drug-induced gingival overgrowth**

Gingival overgrowth or enlargement has been reported in 114 of the 128,000 reports contained in the ADRAC database. Those 114 cases are dominated by the presence of five drugs which account for 68% of the reports, as shown in Table 1.

**Table 1: Reports of Gingival overgrowth**

Drug	Number of Reports
Nifedipine	25
Amlodipine	22
Felodipine	14
Phenytoin	13
Cyclosporin	9

It has been estimated that gingival overgrowth occurs in about 50% of patients taking phenytoin, 25-80% of patients taking cyclosporin, and 15-20% of patients receiving nifedipine, but severe cases with nifedipine occur in less than 1%. ADRAC has received only 2 reports each with diltiazem and verapamil so it is possible that gingival overgrowth is

mainly associated with the dihydropyridine calcium channel blockers (CCBs)

#### References

1. Brunet L, Miranda J, Farré M, Berini L, Mendieta C. Gingival enlargement induced by drugs. Drug Safety 1996; 15: 219-31.
2. Lawrence D, Weart W, Laro JJ, Neville BW. Calcium channel blocker-induced gingival hyperplasia: case report and review of this iatrogenic disease. J Fam Practice 1994; 39: 483-8
3. Johnson RB. Nifedipine-induced gingival overgrowth. Ann Pharmacother 1997; 31: 935.

### **A comparison of dicloxacillin with flucloxacillin**

Early in 1997 dicloxacillin was introduced onto the Australian market to provide an alternative to flucloxacillin in the treatment of staphylococcal infections.

Table below shows the results after the first two calendar years of marketing.

### **Dicloxacillin versus Flucloxacillin in 1997-98**

	Dicloxacillin	Flucloxacillin
Community prescription	493,000	1,182,000
Reports to ADRAC	151	175
Hepatic reactions	24	62
Cholestasis	3	17
Renal reactions	12	4
Intestinal nephritis	5	-

The table shows total reports, reports of hepatic reactions including those of cholestasis, reports of renal reactions and an estimate of community usage.

### **Drugs of Current Interest**

Candesartan (Atacand)	Raloxifene (Evista)
Carvedilol (Dilatrend, Kredex)	Sildenafil (Viagra)
Clopidogrel (Iscover, Plavix)	Tiludronate (Skelid)
Donepezil (Aricept)	Tramadol (Tramal)
Gelatin succinylated (Gelofusine)	Trovafloxacin (Trovan)
Montelukast (Singulair)	Zafirlukast (Accolate)
Naltrexone (ReVia)	Zanamavir (Relenza)
Naratriptan (Naramig)	Zolmitriptan (Zomig)
Nefazodone (Serzone)	

## Canada

Canadian Adverse Drug Reaction Newsletter, Vol. 9, No 2, April 1999

### ***Bupropion (Zyban®), sustained-release tablets): reported adverse reactions***

Bupropion (Zyban®), has been available in Canada since August 1998. Its use is recommended, in combination with the introduction of behavioural changes, to help people quit smoking.

Sustained-release bupropion is also sold under the name Wellbutrin SR® for the relief of symptoms of depression. Between Aug. 18 and Dec. 1, 1998, the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) received 48 reports of suspected adverse reactions to bupropion taken to quit smoking (patients included 15 men, 31 women and 2 people sex unknown; average age 36 [range 27 to 81] years). In the 48 reports, 144 adverse reactions were noted, the most frequent of which were pruritus (9), urticaria (7), edema (7), tremors (6), dizziness (5), insomnia (5) and anxiety (5). Sixteen of the reports described serious events.

There is a risk of convulsions associated with taking bupropion to quit smoking. The CADRMP received 3 reports of convulsions in patients taking Zyban®. One of the patients had a history of alcohol dependence and was taking 600 mg of Zyban® daily for 15 days before experiencing convulsions. In general, convulsions are associated with the Zyban® dose, the use of the drug in conjunction with other drugs and/or the patient's medical history or clinical features.

Adverse cardiovascular reactions were also reported. Patients taking Zyban® experienced palpitations (2), tachycardia (2), angina (1) and myocardial infarction (1). In the last case, a 52-year-old man died following myocardial infarction. He had a history of alcohol dependence and serious coronary artery disease. He had taken 300 mg/d (higher initial dose than that recommended by the manufacturer) for 2 days before he died. The patient was not taking other drugs.

Finally, extreme caution must be observed before administering Zyban® in conjunction with certain other drugs. Two suspected cases of adverse reactions to a bupropion-paroxetine combination were reported. Nausea, vomiting, visual hallucinations and dizziness were reported 2 days after bupropion therapy was started in a 48-year-old woman who had also been taking paroxetine and estrogen replacement therapy for about a year. In the other case, a 27-year-old man experienced tachycardia, anxiety, tremors, mydriasis, blurred vision and photophobia while taking combination therapy with bupropion and paroxetine (duration of therapy unknown). He was also taking clobazam and trazodone.

In both cases, symptoms disappeared after bupropion therapy was stopped.

Bupropion is a new pharmacological alternative for patients who want to quit smoking. It can be used alone or in combination with transdermal nicotine patches; the recommended duration of therapy is 7 to 12 weeks. Bupropion is, however, associated with certain adverse reactions and precautions, which must be observed before administering it. According to the product monograph, the most frequent adverse reactions -- insomnia and dry mouth occur in 31% and 11% of patients respectively. The adverse reactions that most often lead to a cessation of bupropion therapy include central nervous system disturbances (especially tremors) and dermatological reactions.

The combined use of Zyban® and Wellbutrin SR® or any other drug containing bupropion is contraindicated, since the occurrence of convulsions is related to the bupropion dose.

### ***Tolcapone (Tasmar™)***

On Nov. 20, 1998, Health Canada suspended the sale of tolcapone (Tasmar™), the first approved reversible catechol-O-methyl transferase inhibitor indicated as an adjunct to levodopa-decarboxylase inhibitors in the treatment of Parkinson's disease. This action was based on emerging safety concerns regarding hepatotoxicity and potentially fatal fulminant hepatitis associated with tolcapone therapy.

Continued availability of tolcapone through the Special Access Programme (SAP) was organized on a limited and exceptional basis for 1) the safe discontinuation of tolcapone therapy and 2) extraordinary cases involving patients already receiving tolcapone therapy for whom, in the opinion of their physician, the benefits of continued treatment outweighed the risks. As of January 1999, SAP has received about 200 requests for tolcapone.

See also reference from Portugal below.

## Denmark

Ugeskrift for Laeger d. 5. April 1999

### ***Pulmonary oedema after anaesthesia with sevoflurane***

Two cases of lung oedema after anaesthesia with sevoflurane have been reported in Denmark. The first case refers to a 15 years-old boy who was operated and hence put under anaesthesia with sevoflurane. Approximately 100 minutes after awakening the patient was short of breath and pale. Tests showed that he had a pulmonary oedema. He was treated with furosemide and recovered. The second case was similar to the first one.

## New Zealand

Information for Health Professionals, March 1999

### ***Tamoxifen and venous thromboembolism***

Evidence now strongly supports the suspicion that tamoxifen increases the risk of venous thromboembolism (VTE). This observation is consistent with the fact that tamoxifen has oestrogenic activity.

One study, based on a sub-population of 10,000 women with breast cancer, identified 25 cases of VTE with an adequately confirmed diagnosis, and calculated a relative risk of VTE with tamoxifen use of 7.1 (95% CI 1.5-33). Another study used data from a Scottish trial of tamoxifen in the treatment of breast cancer in 1312 women. In this study the risk of VTE in users compared with non-users was higher by a factor of 2.50 (95% CI 1.11-5.56). In addition, the American Breast Cancer Prevention Study involving 13,388 women found the rate of pulmonary embolism among the tamoxifen group to be three times that in recipients of placebo (relative risk 3.01; 95% CI 1.15-9.27).

These results do not greatly affect the benefit-risk assessment for tamoxifen in the treatment of breast cancer. However, women with an elevated risk of breast cancer should not be treated with tamoxifen as a preventive measure (an unapproved indication) without an assessment of the personal risk factors for VTE.

April 1999

### ***Potentially serious adverse effects of carbamazepine: Blood dyscrasias and skin rash***

The Centre for Adverse Reactions Monitoring recently received 3 reports of serious adverse reactions with carbamazepine: severe cholestatic jaundice, Stevens Johnson

syndrome, and multiorgan hypersensitivity with fulminant liver failure resulting in death.

Three published incidence studies have investigated the frequency and seriousness of cutaneous or haematological reactions with carbamazepine. Rash was found to occur in around 10% of patients. Most occurred in the first 2 weeks of treatment and were mild. In each of 2 studies one patient developed a serious reaction - erythema multiforme and Stevens-Johnson syndrome respectively.

Blood dyscrasias (moderate and severe leucopenia and 1 case of thrombocytopenia) occurred with an incidence of 2% with mild changes detected in up to 30% of patients. Most cases developed within the first month of therapy.

To reduce the risk of serious adverse effects, a blood screen and physical examination should be conducted during the first 4-6 weeks of therapy, and repeated where there are clinical reasons for concern. Carbamazepine should be withdrawn or the dose reduced if the white cell count falls below 3000/mm<sup>3</sup> or the neutrophil count below 1000/mm<sup>3</sup>.

May 1999

### ***Clozapine and Hyperglycaemia***

Hyperglycaemia, sometimes leading to ketoacidosis or glycosuria, has been reported in association with clozapine. In some cases the condition has been of new onset, and in others exacerbation of pre-existing diabetes mellitus has occurred. Hyperglycaemia appears to be of early onset (2 weeks to 3 months after initiation of clozapine) and to occur without predisposing factors. Clozapine-induced hyperglycaemia may be serious leading to coma, but it is reversible on discontinuation of clozapine. In some cases continuation of clozapine is possible by controlling serum glucose levels with the use of hypoglycaemic agents. This approach may be useful in refractory schizophrenia responsive to clozapine. In those with diabetes mellitus, glucose monitoring should be conducted in conjunction with the obligatory haematological monitoring. All patients should be advised to report altered consciousness, polyuria or increased thirst.

May 1999

### **Adverse respiratory reactions to long-acting beta-agonists**

There have been occasional reports of deterioration in asthma control, and even respiratory arrest, following the commencement of a long-acting beta-agonist (Serevent, Foradil, Oxis). Several mechanisms need to be considered to explain such reactions including paradoxical bronchospasm, increased bronchial responsiveness and tolerance, but none of these has been identified in prospective studies. Practitioners using long-acting beta-agonists need to be aware of the possibility of such sporadic adverse reactions. Careful monitoring of patients is advised, particularly during the first six weeks of therapy.

### **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:

<b>Medicine</b>	<b>Adverse reactions</b>	<b>Date of addition to list</b>
Alendronate	oesophagitis	April 1998
Carbamazepine	skin and haematological reactions	December 1998
Cisapride	cardiac arrhythmias	May 1999
Clozapine	hyperglycaemia	May 1999
Colchicine	serious toxicity	April 1998
Herbal medicines	all adverse reactions	October 1996
Hormone replacement therapy	venous thromboembolism	April 1998
NSAIDs	renal damage	April 1998
Mefloquine	neuropsychiatric reactions	August 1997
Oral contraceptives	venous thromboembolism	February 1996
Ticlopidine	neutropenia and thrombocytopenia	December 1998

### **Valvular abnormalities with dexfenfluramine and fenfluramine**

In September 1997 dexfenfluramine (Adifax®) and fenfluramine (Ponderax®) were withdrawn from the market world-wide because of a series of cases of valvular abnormalities in individuals who had taken one of these agents in combination with phentermine. More recently, studies have been published demonstrating an association

between echocardiographic valvular abnormalities of the aortic and mitral valves and treatment with dexfenfluramine or fenfluramine alone.

Evidence now favours a causal connection between dexfenfluramine (Adifax) and fenfluramine (Ponderax) when used alone and the development of heart valve abnormalities on echocardiography. Both medicines were withdrawn in 1997. The incidence, severity and likelihood of progression of the valve abnormalities is poorly defined.

The risk appears to be minimal with use < 3 months; most abnormalities were reported as mild. The risk is presently not quantifiable, but appears to increase with duration of use. The major consequence of concern is the development of endocarditis in the damaged valve. As a large number of patients have been exposed to these medications since Ponderax first became available in 1966, and the development of endocarditis is preventable, guidelines have been drawn up in consultation with the Cardiac Society of Australia and New Zealand:

1. Patients who took dexfenfluramine or fenfluramine for < 3 months need not be examined.
2. Those who took either or both agents for 3 months should be examined by a GP for evidence of a heart murmur or other abnormal cardiac signs.
3. If a murmur or other abnormality is found, or the heart cannot be examined due to obesity, refer the patient to a cardiologist for echocardiography.
4. Until a cardiologist is able to advise on the risk of endocarditis, appropriate prophylactic antibiotics should be given to patients requiring dental or other surgical procedures that put them at risk of endocarditis, and
5. Practitioners should send an adverse reaction report for valve abnormalities requiring antibiotic prophylaxis in patients exposed to these medicines to the Centre for Adverse Reactions Monitoring.

### **The medicines currently being monitored are:**

<b>Medicine</b>	<b>Indications/Action</b>
Copper IUCD	IUCD
Eformoterol	Potent long-acting b <sub>2</sub> -agonist
Levonorgestrel intrauterine system	Progestogen-releasing intrauterine system
Montelukast	Antiasthmatic/leukotriene inhibitor

Nefazodone	Antidepressant (5HT <sub>2</sub> blocker)
Olanzapine	Atypical antipsychotic
Quetiapine	Atypical antipsychotic
Salmeterol	Potent long acting b <sub>2</sub> -agonist
Sumatriptan	Migraine relief/selective 5HT <sub>1</sub> -like receptor agonist
Tolcapone	Parkinson's disease

## Portugal

Boletim de FarmacoVigilância Vol 2, No 2, 1998

### *Minocycline – risk of hepatotoxicity and lupus*

Minocycline is a broad-spectrum semi-synthetic tetracycline, widely used as a first line antibiotic in the treatment of acne. Several advantages over other tetracyclines are usually ascribed to minocycline, such as faster absorption; absorption not affected by food; lower intake frequency due to longer half-life; fewer gastrointestinal side-effects; possible efficacy in cases of resistance to tetracyclines in general.

In 1996, given the suspicion of serious adverse reactions – hepatotoxicity and systemic lupus erythematosus (SLE) with higher frequency than with other tetracyclines, the safety profile of minocycline was re-evaluated in the United Kingdom. Thus, adverse hepatic reactions and lupus-like reactions associated with minocycline are rare but can occur with higher frequency than with other tetracyclines. On the other hand, with tetracyclines in general these reactions occur within a period of 6 months from the beginning of therapy (81% in the first 2 weeks), whereas with minocycline only one half of the cases occurred in the first 6 months. Based on the evaluation made it was decided to limit the use of minocycline to 6 month treatments. These should only be continued if a satisfactory response of acne is observed and if liver function tests remain within normal limits.

#### References

1. Gough A, Chapman S, Wagstaff K, Emery P, Elias E – Minocycline induced autoimmune hepatitis and systemic lupus erythematosus-like syndrome. *BMJ* 1996; 312: 169-172.
2. Ferner RE, Moss C – Minocycline for acne. First line antibacterial treatment of acne should be tetracycline or oxytetracycline. *BMJ* 1996; 312: 138.

### *Tolcapone: Marketing suspended*

Tolcapone (Tasmar<sup>®</sup>) is a COMT (Catechol-O-Methyltransferase) inhibitor both at peripheral and central levels. It has been authorised by the European Commission

in August 1997 for the adjuvant treatment of Parkinson's disease, in combination with levodopa/benserazide or levodopa/carbidopa, especially in patients with motor fluctuations (end-of-dose phenomenon) who cannot be stabilised by these associations.

In October 1998, a total of 9 cases of severe hepatic dysfunction (two of which were fatal) had been reported in 100.000 patients treated until then. The EMEA considered that tolcapone could no longer be safely used in clinical practice, given the inability to prevent the development of severe (and even fatal) adverse hepatic reactions by frequent liver function monitoring, and the possible occurrence of neuroleptic malignant-like syndrome and rhabdomyolysis, which had meanwhile also been reported. The risk-benefit ratio of Tolcapone was therefore considered to be unfavourable for the authorised indication. It has not been possible to restrict its indications in such a way as to allow its safe use.

The INFARMED, similarly to the authorities from the other member states, took the necessary measures to suspend Tasmar<sup>®</sup> as of November 1998.

### *Terfenadine 120 mg and association with pseudoephedrine*

Terfenadine is a non-sedative, H<sub>1</sub>-receptor-specific antihistamine. It is known since it was first marketed that it has an arrhythmogenic potential when used simultaneously with certain antifungal agents (imidazoles, such as ketoconazole and itraconazole), or antibiotics (macrolides, like erythromycin or clarithromycin), or still in patients with liver and/or renal failure.

These conditions are associated with an inhibition of terfenadine's main metabolic pathway (isoenzyme CYP3A4 of cytochrome P450) which, under normal conditions, allows terfenadine's levels to remain relatively low. A rise in its plasma concentration may lead to a prolongation of the QT interval with an attendant risk of dysrhythmia.

Terfenadine's safety profile was re-assessed in the EU subsequently to the enforcement of article 12 of Directive 75/319/CE (see Boletim de Farmacovigilância, vol. 1, nº 2). Consequently, two decisions were made concerning medicines containing this active substance.

On the one hand, marketing authorisations for terfenadine in 120 mg-strength tablets and in any strength in association with pseudoephedrine have been withdrawn.

On the other hand, marketing authorisations are kept valid for 60 mg tablets, as well as for the 6 mg/ml oral suspensions. Their SPCs (Summary of Product Characteristics), however, were changed in accordance with the EMEA's advice, emphasising the risk of cardiotoxicity in the Contraindications and in the Drug Interactions section.

### ***Nimesulide Adverse Reactions Reported to the CNF***

Nimesulide is a non-steroid anti-inflammatory (NSAID) sulphonamide whose mechanism of action is characterised by selective inhibition of cyclo-oxygenase 2 (COX2).

This pharmacodynamic profile is compatible with a lower incidence of adverse GI reactions in comparison with other NSAIDs, although this has not been clearly demonstrated. Some studies show that the incidence of this type of ADRs with nimesulide is similar to that of patients treated with a control NSAID. Furthermore, there may appear endoscopically visible lesions of the gastric mucosa with nimesulide, and the selectivity of COX2 inhibition may be lost at higher doses.

The National Pharmacovigilance Centre (CNF) has received, since 1993, 17 ADR reports ascribed to nimesulide. The most frequent ones were skin (5) and liver (4) ADRs. Others were: peripheral oedema (2), stomatitis (2), paresthesia (1), thrombocytopenic purpura (1), irritability (1), and headaches/ reduced visual acuity (1). No adverse GI reactions have been reported. The adverse skin reactions reported included three cases of rash, one case of urticaria/angioedema, and one case of necrotising fasciitis which evolved to septicaemia and death. Except for the case of necrotising fasciitis, these ADRs have been previously described with the administration of nimesulide. Several cases of necrotising fasciitis are described in association with various NSAIDs, but this association has never been clearly demonstrated. Of the hepatic ADRs reported, two cases were compatible with Reye's syndrome. They occurred in children and were both fatal. One case of cholestasis, and another of liver enzyme elevation and coagulopathy were also reported, the latter being fatal. Liver enzyme elevation and acute hepatitis in patients on nimesulide are mentioned in the literature.

In the cases reported to the CNF, all patients were concomitantly medicated with amoxicillin+clavulanate. Similarly, one of the patients who died of Reye's syndrome had also been given lysine salicylate. Although the reporting professionals ascribed a causal relationship to nimesulide, one cannot firmly exclude the direct role of the amoxicillin+clavulanate association in causing liver damage, whose occurrence has been described with the use of this antibiotic (see Vol.1, n.o 4). On the other hand, it is not known whether there may be an interaction between nimesulide and amoxicillin+clavulanate which may potentiate the hepatic dysfunction induced by any one of these drugs.

## **Sweden**

Information from the MPA, Vol 10, No 1, 1999

### ***Acute renal failure and quinine***

A 57-year-old woman on naproxen and aceclofenac started treatment with quinine 100 mg due to nightly akathisia. Two days later she experienced abdominal pain and vomiting. The next day she had diarrhoea, yellow eyeballs and dark urine. Laboratory tests showed increased level of creatinine, decreasing diuresis, thrombocytopenia and mild anaemia. The doctor suspected NSAID induced renal failure and all drugs were suspended. There was no evidence of renal necrosis. She underwent dialysis once. One month later her renal function was normalised. A short time after she took quinine 100 mg. A couple of hours later she had fever, diarrhoea, vomiting and acute renal failure. Between these two incidences she had had diarrhoea and nausea when drinking Tonic water containing quinine.

### ***Donepezil - possible hepatotoxicity***

Donepezil is a selective acetylcholine inhibitor used for treatment of Alzheimer's disease. Some of the known adverse reactions are: insomnia, diarrhoea, anorexia, syncope, bradycardia and AV-block. The drug was approved in Sweden in July 1997. During review of ADR reports, several cases of suspected liver reactions were found. According to the manufacturer more than 500 000 patients have been treated. 50 patients have had liver or biliary reactions. The MPA doesn't think it is motivated to monitor the liver status continuously but asks doctors to investigate possible liver reactions in patients taking donepezil and to report them to the MPA.

### ***Tinidazole and liver damage***

In 1997 a 37-year-old man stayed several months in Africa. He took proguanil and chloroquine for malaria prophylaxis. When he returned to Europe he received tinidazole and possibly also metronidazole due to diarrhoea. A short time after he was hospitalized due to signs of icterus. Drug induced hepatitis was confirmed by laboratory tests and liver biopsy. In 1998 the man once more returned from Africa and received tinidazole for diarrhoea. A week later he noticed dark urine, fatigue, weight loss and vomiting. Toxic liver damage was suspected but no liver biopsy was taken. In 1999 he had recovered completely.

### ***Nefazodone - a serious case of fulminant liver damage***

A woman aged 44, with one previous episode of depression started treatment with nefazodone 200 mg daily. After one month the dose was 400 mg daily. After three months the dose was decreased to 300 mg daily. The patient didn't receive any other medication during that time. After three months she experienced nausea, blurred vision and coldness. The symptoms continued and the fatigue increased. When her husband saw that she had yellow eyeballs she was submitted to hospital where it was confirmed that she had acute liver damage. The patient's condition rapidly got worse. She was unconscious and put in a respirator. Lab-tests, anamnesis and course of event pointed towards drug induced fulminant liver damage. The patient underwent two liver transplantations but died later on.

### ***Latanoprost and trichiasis***

Two cases of trichiasis in patients treated with latanoprost for glaucoma has been reported to the Medical Products Agency. In total, the MPA has received 43 reports for latanoprost of which 17 concerned eye reactions. Of these 17 reports, 11 referred to longer, darker and more marked eyelashes.

## **USA**

FDA Talk paper, May 12, 1999

### ***New warning for arthritis drug, Enbrel***

Enbrel was approved last November with labeling that says that it should not be given to patients with sepsis and should be discontinued if a patient develops a serious infection.

FDA is advising physicians about new safety concerns regarding the use of etanercept (Enbrel), a product recently approved to treat moderate to severe rheumatoid arthritis (RA). New postmarketing reports indicate that certain patients receiving Enbrel have developed serious infections, including sepsis, and that several of these patients have died from their infections.

## **DRUG WITHDRAWALS**

### **EMEA**

London, 11 June 1999

### ***EMEA public statement on Trovan/Trovan IV/Turvel/Turvel IV***

The European Commission granted marketing authorisations for the whole European Union to Pfizer Limited on 3 July 1998 for Trovan® (trovafloxacin) and Trovan IV® (alatrofloxacin) and to Roerig Farmaceutici Italiana S.p.A. on 8 July 1998 for Turvel® (trovafloxacin) and on 3 July 1998 for Turvel IV® (alatrofloxacin).

The Scientific Committee for Proprietary Medicinal Products (CPMP) of the European Medicines Evaluation Agency (EMEA) during its extraordinary meeting on 10 June 1999, has adopted an Opinion recommending the suspension of the marketing of Trovan/Trovan IV and Turvel/Turvel IV. This was due to increased concern over 152 documented reports of cases of serious hepatic events, including 9 cases where patients died or required a liver transplant.