COMMITTEE ON SAFETY OF MEDICINES

# CURRENT PROBLEMS in Pharmacovigilance

MEDICINES CONTROL AGENCY

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***Internet version: http://www.mca.gov.uk/ourwork/monitorsafequalmed/currentproblems/currentproblems.htm***

## Inhaled corticosteroids and adrenal suppression in children

*Adrenal suppression may be under-recognised*

Adrenal suppression is a well-established adverse reaction of all inhaled corticosteroids[1]. There have been rare reports of adrenal suppression leading to adrenal crisis. Symptoms and signs associated with adrenal suppression and crisis may be under-recognised, particularly in children receiving higher than licensed doses of inhaled corticosteroids. The MCA/CSM have recently reviewed evidence relating to adrenal suppression and crisis in children following the use of inhaled corticosteriods including fluticasone. This review included spontaneously reported adverse drug reactions through the Yellow Card Scheme, published literature[2] and a recent national (UK) survey of adrenal crisis due to inhaled corticosteroids[3].

Prescribers are reminded that the presenting symptoms of adrenal suppression and crisis are non-specific and include **anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, decreased level of consciousness, hypoglycaemia and seizures. Situations which may potentially trigger acute adrenal crisis include infection, trauma, surgery or any rapid reduction in dosage.**

Adrenal suppression is a dose-related class effect of all inhaled corticosteroids. Adrenal crisis has been observed more frequently following the use of fluticasone, possibly because higher than licensed doses of fluticasone are prescribed more widely in children than other inhaled corticosteroids. All inhaled corticosteroids are associated with an increased risk of adrenal crisis when used at higher than licensed doses but prescribers are reminded that fluticasone should normally be used at half the dose of beclomethasone (CFC containing) or budesonide because of its greater potency.

Although case reports have highlighted children taking fluticasone at higher than recommended doses (typically ≥ 1000 micrograms/day of fluticasone), prescribers are reminded that these are dose related class effects, and are strongly advised that the paediatric licensed dosages (see Box 1) of all inhaled corticosteroids should not be exceeded.

Prescribers are reminded that:

- It is important to review therapy regularly and titrate down to the lowest dose at which effective control of asthma is maintained.
- If a doctor considers that a child's asthma is not controlled on the maximum licensed dose of their inhaled corticosteroid, despite the addition of other therapies, the child should be referred to a specialist in the management of paediatric asthma.

**Box 1: Maximum licensed doses of inhaled corticosteroids in children**

| | |
|---|---|
| **Beclomethasone** | 400 mcg/day, age not stated |
| **Budesonide** | 800 mcg/day (under 12 years) |
| **Fluticasone** | 400 mcg/day (4 - 16 years) |

1. CSM/MCA *Current Problems in Pharmacovigilance* 1998; 24: 8
2. Drake A.J. et al. BMJ 2002; 324(7435): 1091-1083
3. Zahra S et al. Arch Dis Child 2002; 86 Suppl 1: A39

## New advice on aspirin in under 16s

Do not give aspirin to children under 16 years (unless specifically medically advised). Further information available on the website www.mca.gov.uk

## Clozapine and cardiac safety: updated advice for prescribers

*Patients who develop clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine*

Clozapine is an atypical antipsychotic agent contraindicated in patients with severe cardiac disorders. An increased incidence of myocardial disease in clozapine (Clozaril) users has been recognised for some years and information for prescribers has been updated accordingly. A recent re-evaluation of serious adverse cardiac events in association with use of clozapine has resulted in a strengthening of these warnings.

Before starting clozapine therapy, patients are required to undergo a history and physical examination. Patients with a history of cardiac illness or abnormal cardiac findings on physical examination should be referred to a specialist for other examinations that might include an ECG and echocardiogram, and clozapine should only be initiated if severe heart disease is excluded and the benefits of treatment are considered to clearly outweigh the risks. The prescribing doctor should consider performing a pre-treatment ECG to allow comparisons if symptoms develop later.

Rare cases of myocarditis have been reported, some of which have been fatal. Post-marketing experience suggests that the increased risk of myocarditis occurs most commonly in the first 2 months of treatment. Very rare cases of cardiomyopathy have also been reported; these cases generally occurred later in treatment and some were fatal. Pericarditis and pericardial effusion have also been associated with clozapine treatment.

Tachycardia is a common side effect of clozapine treatment that occurs in about 25% of users, especially during dose titration in early treatment. However, it is also a key symptom of myocardial disease. It is therefore essential that patients who have *persistent* tachycardia at rest, especially in the first 2 months of treatment, are closely observed for other signs and symptoms of myocarditis/ cardiomyopathy. These include palpitations, arrhythmias, symptoms mimicking myocardial infarction, chest pain and other unexplained symptoms of heart failure.

A minority of clozapine-treated patients experience ECG changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T waves, which normalise after discontinuation of clozapine. The clinical significance of these changes is unclear. However, such abnormalities have been observed in patients with myocarditis, which should therefore be considered. If clozapine-induced myocarditis or cardiomyopathy is suspected, clozapine treatment should be discontinued promptly and the patient referred urgently to a cardiologist for diagnostic evaluation.

**Patients who have developed clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine.**

**Key information for prescribers:**

- Patients must have a history and physical examination prior to starting therapy. The treating physician should consider performing a pre-treatment ECG.
- Patients who have *persistent* tachycardia at rest, especially during the first two months of treatment, should be closely observed for other signs or symptoms of myocarditis or cardiomyopathy. These include palpitations, arrythmias, symptoms mimicking myocardial infarction, chest pain and other unexplained symptoms of heart failure.
- Patients in whom myocarditis or cardiomyopathy is suspected should stop clozapine and undergo urgent diagnostic evaluation by a cardiologist.
- Patients with clozapine-induced myocarditis or cardiomyopathy must not be re-exposed to clozapine.

## HMG CoA Reductase Inhibitors (statins) and myopathy

*Proven benefits outweigh low risk of myopathy*

HMG CoA reductase inhibitors, commonly referred to as the statins, are used as the treatment of choice for hypercholesterolaemia, which is a major risk factor for coronary artery disease. Large-scale, long-term studies (WOSCOPS[1], CARE[2], LIPID[3] [pravastatin], 4S[4] [simvastatin]) clearly demonstrate the beneficial effect of statins in reducing morbidity and mortality from coronary artery disease.

The most common adverse reactions of the currently marketed statins are relatively non-serious and transient in nature, and include gastrointestinal disturbances, headache and sleep disorders. Rare but clinically important adverse effects are elevations in hepatic transaminases, peripheral neuropathy and myopathy, including rhabdomyolysis.

Cerivastatin (Lipobay) was withdrawn in August 2001 due to an unacceptably increased risk of rhabdomyolysis, particularly when used in combination with gemfibrozil. This prompted a Europe wide review of the risk of myopathy in association with the remaining statins, which concluded that the overall risk of myopathy is low (occurring in less than 0.5% of patients) and rhabdomyolysis occurs rarely with the statins currently marketed.

Due to pharmacokinetic and lipophilicity differences, the

potential for inducing muscle disorders varies with individual drugs. The exact mechanism by which statins cause rhabdomyolysis remains unclear. However, it appears to be dose-dependent. High doses and/or drug interactions which increase statin plasma levels and hence statin exposure appear to lead to increases in adverse muscle events, which may be related to an increased inhibition of HMG-CoA reductase within the myocyte.

The main risk factors for developing myopathy include:

- Underlying muscle disorders, renal impairment, hypothyroidism or alcohol abuse.

- Concomitant use of other lipid lowering agents i.e. gemfibrozil, other fibrates or nicotinic acid.

- Concomitant use of cytochrome P450 3A4 inhibitors including cyclosporin, macrolide antibiotics (e.g. erythromycin and clarithromycin), azole antifungals (e.g. itraconazole and ketoconazole) and protease inhibitors (e.g. nelfinavir, indinavir and ritonavir).

In order to reduce the risk of myopathy with HMG CoA reductase inhibitors, the Committee on Safety of Medicines recommends that:

- Dosage instructions should be strictly adhered to (see product information). The maximum recommended dosage should not be exceeded and any adjustment of dosage should be made at intervals of 4 weeks or more.

- Careful consideration should be given to statin use in patients who are at an increased risk of developing myopathy (see above). Baseline measurement and monitoring of creatine kinase (CK) should be considered in these patients. If CK is >5 times the upper limit of normal (ULN) at baseline, treatment should not be started.

- Patients are made aware of the risk of myopathy, including rhabdomyolysis, and asked to report promptly any muscle pain, tenderness or weakness, especially if accompanied by malaise, fever or dark urine.

- Patients experiencing muscle pain, weakness or cramps whilst on treatment should have their CK level measured. If this is significantly elevated (>5x ULN) or if myopathy is suspected, treatment should be stopped, while the patient is adequately monitored for muscular symptoms and cardiovascular risk.

- If the symptoms resolve and CK levels return to normal, re-introduction of the statin or introduction of an alternative statin may be considered. This should be initially at the lowest dose and with close monitoring.

The rare risk of myopathy must be considered in the context of the overwhelmingly beneficial effects of the statins in the prevention of coronary artery disease. These benefits clearly outweigh the potential risks.

Please continue to report suspected adverse drug reactions to the statins through the Yellow Card Scheme.


1. Shepherd J et al. N Eng J Med 1995; 333: 1301-1307.
2. Sacks FM et al. N Eng J Med 1996; 335: 1001-1009.
3. LIPID study group. N Eng J Med 1998; 339: 1349-1357.
4. Scandinavian Simvastatin Survival Group. Lancet 1994: 344: 1383-1389.


## Cyproterone acetate (Dianette): Risk of venous thromboembolism (VTE)

*It should only be used to treat severe acne and hirsutism.*

Dianette is indicated for women with severe acne which has not responded to oral antibiotics, or for moderately severe hirsutism. It contains cyproterone acetate (2mg), an anti-androgenic progestogen, and ethinylestradiol (35μg) and it is administered for 21 days of each menstrual cycle. It therefore has a similar composition to that of a combined oral contraceptive (COC) and provides effective contraception.

However, Dianette is **not** authorised for the sole purpose of oral contraception and should be discontinued 3 to 4 menstrual cycles after the woman's androgen-related condition has completely resolved. The use of a COC carries an increased risk for venous thromboembolism (VTE), including deep venous thrombosis and pulmonary embolism, compared with no use.

Epidemiological studies have shown that the incidence of VTE in users of oral contraceptives with low oestrogen content (<50μg ethinylestradiol) is up to about 40 cases per 100,000 women-years. This compares with 5-10 cases per 100,000 women-years for non-users of COCs and 60 cases per 100,000 pregnancies.

There is some epidemiological evidence that the incidence of VTE in users of Dianette is higher than in users of low-dose oestrogen COCs[1-4]. A recent case-control study using the UK General Practice Research Database (GPRD) found a four-fold increase in the risk of VTE in 24,401 women taking oral contraceptives that contain cyproterone acetate/ethinylestradiol compared with 75,000 women taking second generation oral contraceptives that contain levonorgestrel/ethinylestradiol[1].

In the UK, Dianette usage has increased in recent years. Women with androgen-related conditions may have an inherently increased cardiovascular risk. Product information is being updated to reflect these new findings.

**Prescribers are reminded that:**

- Dianette is **not** indicated for use solely as an oral contraceptive.
- Dianette is a treatment for women with severe acne that has not responded to oral antibiotics, or for moderately severe hirsutism.
- Dianette should be withdrawn 3 to 4 cycles after the treated condition has completely resolved.
- The incidence of VTE in Dianette users is higher than that in women who use low-dose oestrogen COCs.
- Dianette is contraindicated in women with a personal or close family history of confirmed, idiopathic VTE and in those with a known current venous thrombotic or embolic disorders.
- Women who have severe acne or hirsutism may have an inherently increased cardiovascular risk.


1. Vasilakis-Scaramozza C and Jick H. Lancet 2001; 358: 1427-29.
2. WHO Study. Lancet 1995; 346: 1582-88.
3. Pini M et al. Rec Prog Med 1996; 87(7/8): 331-7.
4. Parkin L et al. Lancet 2000; 355: 2133-4.


## Tamoxifen and venous thromboembolism

*New advice for patients with breast cancer and anovulatory infertility*

Tamoxifen is an oestrogen receptor antagonist that is used to treat oestrogen receptor positive breast cancer and anovulatory infertility. The International Breast Cancer Intervention Study (IBIS) which investigated the use of tamoxifen in the unlicensed indication of breast cancer prevention, has confirmed that tamoxifen-treated women have approximately a 2.3 fold higher risk of venous thromboembolism (VTE) than those treated with placebo. Approximately 40% of the VTE cases occurred within 3 months of surgery or following immobility.

In March 2002, the IBIS study Chairman made public his recommendations that women should no longer be treated with tamoxifen for the **prevention** of breast cancer (i.e. the prevention of occurrence rather than the management of diagnosed disease) and the Department of Health issued an Epinet message to all health care providers (www.doh.gov.uk/cmo/cmo02_04.htm).

The Committee on Safety of Medicines (CSM) has subsequently considered how the risk of VTE should best be managed in patients who are using tamoxifen for the licensed indications of the **treatment** of breast cancer or anovulatory infertility. CSM's recommendations are detailed in the table below. Since the balance of risks and benefits for the two patient groups are very different, the advice is indication-specific. Product information for prescribers and patients is being updated accordingly.

**Breast cancer treatment**

*Prior to starting treatment with tamoxifen*

- Obtain a careful personal and family history of VTE.
- The decision to treat should be based on the overall risk to the patient.
- Use of prophylactic anticoagulant may be justified.

*Surgery/ immobility*

- Do not stop tamoxifen treatment before surgery or long-term immobility unless the risk of tamoxifen-induced thrombosis clearly outweighs the risk of interrupting treatment.
- This decision should take into account the possible duration of treatment interruption, the stage and grade of cancer, the clinical response of the patient to tamoxifen therapy and the stage of the treatment regimen at which the interruption occurs.
- All patients should receive appropriate thrombosis prophylactic measures.

*Occurrence of VTE*

- Stop tamoxifen immediately and initiate anti-thrombosis measures.
- The decision to re-start tamoxifen should be made with respect to the overall risk:benefit balance for the patient.
- Anti-coagulation measures should be considered if the patient is to be restarted on tamoxifen.

**Anovulatory infertility**

*Prior to starting treatment with tamoxifen*

- Tamoxifen is contraindicated in patients with known personal or family history of confirmed, idiopathic VTE or known genetic defect that predisposes to thrombophilia.

*Surgery/ immobility*

- Stop tamoxifen treatment at least 6 weeks before surgery or long-term immobility and re-start only when the patient is fully mobile.
- All patients should receive appropriate thrombosis prophylactic measures.

*Occurrence of VTE*

- Stop tamoxifen immediately and initiate appropriate anti-thrombotic measures.
- Do not re-start tamoxifen unless there is a compelling alternative explanation for the thrombotic event.

## Safety update on long-term HRT

**In April we informed you of updated product information for HRT[1]. Since then the recent early termination of one part of a major trial[2] into the risks and benefits of long-term combined HRT has prompted a re-examination of its safety.**

The Committee on Safety of Medicines (CSM) and its Expert Working Group on HRT have now carefully considered the data from recent studies[2,3,4,5]. These have demonstrated that the types of HRT studied (see table 1): do not prevent coronary heart disease (CHD), confirmed previous estimates of the increased risks associated with HRT for breast cancer[6] and venous thromboembolism (VTE) and identified an increase in the risk of stroke.

Additionally, a number of observational studies[7,8,9] in oestrogen-only HRT users have suggested an increased risk of ovarian cancer. The absolute incidence of any of these conditions is generally small (see table 2), but most increase with increasing duration of HRT use.

The randomised controlled trial (RCT) findings mostly relate to the use of one particular HRT regimen (see below) and comparable long-term safety data for other HRT regimens are less complete.

***From the evidence currently available, it is not known whether all the risks outlined below extend to other HRT products, although the available data do not suggest substantial variation between products.***

**Implications for prescribing**

- For short-term (eg 2 to 3 years) use of HRT for the relief of menopausal symptoms, the benefits are considered to outweigh the risks for most women who use it.

- Longer term use of HRT is licensed for the prevention of osteoporosis. However, patients should be aware of the increased incidence of some conditions with long-term HRT use and of alternative treatment options for the prevention of osteoporosis.

- The decision to use HRT should be discussed with each woman on an individual basis, taking into consideration her history, risk factors and personal preferences.

- In addition, an individuals risks and benefits should be regularly reappraised (eg at least yearly) with continued HRT use.

- HRT should not be prescribed for prevention of CHD.

**The evidence considered**

Two of the RCTs, WHI[2] and HERS/HERS II[3,4] used a specific combination of continuous oral conjugated equine oestrogen (CEE, 0.625mg) plus medroxyprogesterone acetate (MPA, 2.5mg), similar to Premique (CEE, 0.625mg + MPA, 5mg), in apparently healthy women and in women with previous CHD, respectively.

These trials had an average follow-up period of about 5 years. The WEST trial[5] used oral oestrogen-only HRT (17β-oestradiol, 1mg) and examined death or recurrence of stroke in post-menopausal women who had recently had an ischaemic stroke or transient ischaemic attack.

The **key findings** for *long-term* use of these particular HRT regimens are:

- **Coronary Heart Disease**:
  The anticipated benefit of long-term HRT use in preventing CHD, as suggested by observational studies, has not been supported by the RCT data[2,3,4]. The trials have shown a possible increase in the risk of CHD in the first year of HRT use and no evidence for benefit thereafter both for women with and those without a history of CHD. No HRT product is licensed for prevention of CHD.

- **Stroke**:
  Overall results from RCTs[10] have shown an increase in the risk of stroke in HRT users. For women in the age range 50-59, this would mean about 1 extra stroke per 1000 women using HRT for 5 years.

  For women who take HRT for 5 years between the ages of 60 and 69, this would mean about 4 extra strokes per 1000 women, because of the increased risk of stroke with age. The previous observational data were inconsistent on the risk of stroke in HRT users.

- **Venous Thromboembolism (VTE)**:
  The baseline risk of VTE in non-HRT users between the ages of 50 and 70 is higher than previously estimated, so the absolute risk associated with HRT is also higher (see Table 2). Note, for consistency, these risks are now presented over 5 years.

- **Breast Cancer**:
  The known increased risk of breast cancer in HRT users has been confirmed. There is no change in the estimated numbers of excess cases (see Table 2).

In addition, observational studies[7,8,9] suggest that:

- **Ovarian Cancer**:
  Results indicate a small increased risk of ovarian cancer in hysterectomised women with long-term use of oestrogen-only HRT. The risks of ovarian cancer with combined HRT are unclear.

**Table 1. Randomised trials** (adapted from[10]).

| Study name | Women recruited | Number randomised* | Duration of follow up | Comments |
|---|---|---|---|---|
| HERS[a] | women with previous heart disease | 2763 | 4.1 years | Multicentre, US, trial; HERSII Additional 2 years follow up of open label continuation; main results published[3,4] |
| WEST[b] | women with previous stroke | 664 | 2.8 years | Multicentre, US trial;main results published[5] |
| WHI[c] | healthy women with an intact uterus | 16608 | 5.2 years | Multicentre, US trial; terminated early; main results published[2] |

a) Heart and Estrogen/ progestagen Replacement Study b) Women's Estrogen for Stroke Trial c) Women's Health Initiative
*approximately equal numbers randomized to placebo and active treatment in each trial.

**Table 2: Summary of possible risks[a] associated with using HRT.**

| Condition | Age of woman (yr) | Number of cases in 1000 non-HRT users | Extra number of cases in 1000 HRT users over the same period | | |
|---|---|---|---|---|---|
| **Cumulative cancer risk (ages 50 to 70)** | | | **5 years use** | **10 years use** | **15 years use** |
| Breast cancer | 50-69 | 45 | 2 (±1) | 6 (±3) | 12 (±8) |
| Ovarian cancer[b] | 50-69 | 9 | 1 (±1) (oestrogen-only HRT) | 3 (±2) (oestrogen-only HRT) | |
| **Cardiovascular risks over 5 years** | | | | | |
| Stroke | 50-59<br>60-69 | 3<br>11 | 1 (±1)<br>4 (±3) | | |
| VTE | 50-59<br>60-69 | 3<br>8 | 4 (±2)<br>9 (±5) | | |
| **Benefits over 5 years** | | | **Reduced number of cases in 1000 HRT users over the same period** | | |
| Colorectal cancer | 50-59<br>60-69 | 3<br>8 | 1 (±1)<br>3 (±2) | 2 (±2)<br>5-6 (±4) | |
| Fracture of neck or femur | 50-59<br>60-69 | 1-2<br>7-8 | 0-1 (±1)<br>2-3 (±2) | 1 (±1)<br>5 (±3) | |

Numbers are best estimates (± approximate range from 95% Confidence Intervals).
[a] Risks have been calculated over 20 year or 5 year period per 1000 women with 5 or 10 years of HRT use rather than incidence per 10,000 women *per year* for ease of understanding. Sources of data: breast cancer[6]; ovarian cancer[11]; stroke and VTE[10] based on [2];
[b] The risks of ovarian cancer with combined HRT are unclear.

***A more detailed version of this article and an information sheet for patients is also available on the MCA website (***www.mca.gov.uk***)***


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## Withdrawal of Epogam and Efamast

*Therapeutic efficacy unproven*

The product licences for Epogam and Efamast, are being withdrawn with effect from 7 October 2002. No new stock will be supplied after 7 October 2002.

Evening Primrose Oil is still available in health food shops for those who wish to take it as a dietary supplement. Patients taking Epogam or Efamast should have the management of their condition reviewed at their next routine visit. Further information can also be found on the MCA website www.mca.gov.uk


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