

Drug Safety Update



Latest advice for medicines users

The monthly newsletter from the **Medicines and Healthcare products Regulatory Agency** and its independent advisor the **Commission on Human Medicines**

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Welcome to the second issue of *Drug Safety Update*.

This month's bulletin includes important drug safety advice for hormone-replacement therapy (HRT, page 2). We have put together a digested guide of current evidence for the associations between HRT and coronary heart disease; stroke; venous thromboembolism; and cancers of the breast, endometrium, or ovary. We hope that this updated information, including revised risk estimates, will help healthcare professionals assess the risks and benefits associated with HRT for individual women.

On page 5 we discuss the balance of benefits and risks for tibolone—a first-line treatment for menopausal symptoms and a second-line therapy for prevention of osteoporosis—and give updated clinical advice for this medicine.

We wish to remind healthcare professionals about the important side-effect profile associated with corticosteroids (page 9).

We hope that you find this issue of *Drug Safety Update* a useful source of information. Please share your thoughts on the bulletin with us by completing the survey online at <http://www.mhra.gov.uk/mhra/drugsafetyupdate>, or by emailing drugsafetyupdate@mhra.gsi.gov.uk

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The Medicines and Healthcare products Regulatory Agency is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe.

The Commission on Human Medicines gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

Drug safety advice

Hormone-replacement therapy: updated advice

Keywords: hormone-replacement therapy, coronary heart disease, stroke, venous thromboembolism, endometrial cancer, breast cancer, ovarian cancer, premature menopause, oestrogen, progestogen

Before prescribing hormone-replacement therapy, healthcare professionals should consider carefully the potential benefits and risks for every woman

For further information, access the Public Assessment Report at http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodetd=230

1 Current Problems in *Pharmacovigilance* 2004; **30**: 4–7. http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON007447&ssTargetNodeid=368

2 Rossouw JE. *JAMA* 2007; **297**: 1465–77.

3 Grady D, et al. *JAMA* 2002; **288**: 49–57.

4 Hendrix SL, et al. *Circulation* 2006; **113**: 2425–34.

5 Wassertheil-Smolter S, et al. *JAMA* 2003; **289**: 2673–84.

6 Grodstein F, et al. *Ann Intern Med* 2000; **133**: 933–41.

7 Lemaitre RN. *Arch Intern Med* 2006; **166**: 399–404.

Since the publication of information about hormone-replacement therapy (HRT) in *Current Problems in Pharmacovigilance* in October, 2004,¹ important new evidence has become available that affects prescribing advice.

Menopausal symptoms

HRT effectively relieves vasomotor symptoms. In most cases, 2–3 years' therapy is sufficient, but some women may need longer—this judgement should be made on a case-by-case basis with regular attempts to discontinue. Symptoms may recur for a short time after stopping HRT.

For all women, the lowest effective dose should be used for the shortest time.

Coronary heart disease (CHD)

Randomised controlled trials have found an increased risk of CHD in women who started combined (oestrogen-progestogen) therapy more than 10 years after menopause.^{2,3} Very few randomised controlled trials have assessed younger, newly menopausal women, and some have suggested a lower relative risk in these women compared with older women. The low baseline risk of CHD in most younger women, and the very low attributable risk due to HRT, means that their overall CHD risk is likely to be low. No increased risk of CHD with use of oestrogen-only HRT has been identified to date.² Importantly, there are no data from randomised controlled trials to suggest a cardiovascular benefit with oestrogen-only or combined HRT.

Healthcare professionals should assess carefully every woman's risk of CHD before prescribing HRT, irrespective of her age or time since menopause.

Stroke

In randomised controlled trials, oestrogen-only and combined HRT increased the risk of stroke (mostly ischaemic) compared with placebo.^{4,5} Although the increase in relative risk seems to be similar irrespective of age,² baseline risk of stroke increases with age and therefore older women have a greater absolute risk. Limited observational data suggest that this risk may depend on oestrogen dose.^{6,7}

8 Peverill RE. *Best Pract Res Clin Endocrinol Metab* 2003; **17**: 149–64.

9 Scarabin P-Y. *Lancet* 2003; **362**: 428–32.

10 Grady D, et al. *Obs Gynae* 1995; **85**: 304–13.

11 Million Women Study Collaborators. *Lancet* 2005; **365**: 1543–51.

12 Shah NR, et al. *Menopause* 2005; **12**: 668–78.

13 Stefanick ML. *JAMA* 2006; **295**: 1647–57.

14 Anderson GL. *Maturitas* 2006; **55**: 103–15.

15 Beral V. *Lancet* 2007; **369**: 1703–10.

16 Danforth KN. *Br J Cancer* 2007; **96**: 151–56.

Venous thromboembolism (VTE)

Oral HRT has been associated with an increased risk of VTE (ie, deep vein thrombosis or pulmonary embolism) in randomised controlled trials and observational studies. Evidence suggests that risk is higher with combined HRT than with oestrogen-only HRT, and that these events are more likely in the first year of use.⁸

The level of risk associated with other routes of administration has not been clearly established, although it may be lower with transdermal HRT.⁹

Endometrial cancer

In women with a uterus, use of oestrogen-only HRT substantially increases the risk of endometrial hyperplasia and carcinoma in a way that depends on dose and duration.¹⁰ Addition of progestogen cyclically for at least 10 days per 28-day cycle greatly reduces the risk, and addition of progestogen every day eliminates the risk.¹¹

Breast cancer

The risk of breast cancer is increased in women who take HRT for several years:

- Combined HRT has been associated with the highest risk
- For oestrogen-only HRT, risk is lower than with combined HRT.¹² Some studies have not shown an increased risk for oestrogen-only HRT¹³
- Risk increases with duration of use and returns to baseline within a few years of stopping treatment

HRT, especially combined therapy, may increase mammographic density, which may adversely affect radiological detection of breast cancer. In the Women's Health Initiative trial,^{13,14} conjugated equine oestrogens (CEE) and CEE plus medroxyprogesterone increased the likelihood of having an abnormal mammogram that needed further evaluation.

Ovarian cancer

Observational studies suggest that long-term use of oestrogen-only or combined HRT may be associated with a small increased risk of ovarian cancer, which returns to baseline a few years after stopping treatment.^{15,16}

Osteoporosis

HRT is effective for prevention of osteoporosis, but its beneficial effect on bone diminishes soon after stopping treatment.

Because of the risks associated with long-term use, HRT should be used for prevention of osteoporosis only in women who are unable to use other medicines that are authorised for this purpose.

Advice for healthcare professionals to consider before prescribing HRT:

- The decision to prescribe HRT should be based on a thorough evaluation of the potential benefits and potential risks of treatment
- Healthcare professionals should assess every woman's overall risk, including cardiovascular risk, particularly in those older than 60 years who have increased baseline risk of serious adverse events
- Evidence for the risks of HRT in women who had premature menopause is limited. However, the baseline risk of adverse events in these younger women is low, and the balance of benefits and risks may be more favourable than in older women

Age range (years)	Time (years)	Background incidence per 1000 women in Europe*	Oestrogen-only HRT		Oestrogen-progestogen HRT	
			Additional cases per 1000 HRT users†	Risk ratio (95% CI)‡	Additional cases per 1000 HRT users†	Risk ratio (95% CI)‡

* Background incidence from: Hospital Admissions in England (HES) for stroke and VTE; WHI trial for CHD; the International Agency for Research on Cancer (IARC) for ovarian cancer and endometrial cancer; and from never-users in the Million Women Study for breast cancer.

† Best estimate and range based on relative risk and 95% CI.

‡ Risk ratios and 95% CI from: meta-analyses of randomised controlled trials (RCTs) for stroke; meta-analyses of RCTs and observational studies for VTE, endometrial cancer, and ovarian cancer; meta-analysis of RCTs and observational studies in Europe only for breast cancer; and from Women's Health Initiative (WHI) trial for CHD.

§ European studies have generally identified higher breast-cancer risk than North American studies and may be due to differences in prevalence of obesity.

|| Progestogen added for 10 days or more per 28-day cycle.

¶ Estimates from placebo groups from the conjugated equine oestrogens (CEE) and CEE plus medroxyprogesterone placebo arms of WHI trial.²

** Menopausal symptom relief is not included in this table, but is a key benefit of HRT and will play a major part in the decision to prescribe HRT.

NS non-significant difference.

O+P oestrogen-progestogen.

Cancer risk

Breast[§]

50-59	5	10	2 (1-4)	1.2 (1.1-1.4)	6 (5-7)	1.6 (1.5-1.7)
60-69	5	15	3 (2-6)		9 (8-11)	
50-59	10	20	6 (4-10)	1.3 (1.2-1.5)	24 (20-28)	2.2 (2.0-2.4)
60-69	10	30	9 (6-15)		36 (30-42)	

Endometrial

50-59	5	2	4 (3-5)	3.0 (2.5-3.6)	NS	1.0 (0.8-1.2)
60-69	5	3	6 (5-8)		NS	
50-59	10	4	32 (21-48)	9.0 (6.3-12.9)	NS	1.1 (0.9-1.2)
60-69	10	6	48 (32-71)		NS	

Ovarian

50-59	5	2	<1	1.1 (1.0-1.3)	<1	1.1 (1.0-1.3)
60-69	5	3	<1		<1	
50-59	10	4	1 (1-2)	1.3 (1.1-1.5)	1 (1-2)	1.3 (1.1-1.5)
60-69	10	6	2 (1-3)		2 (1-3)	

Cardiovascular risk

Venous thromboembolism (VTE)

50-59	5	5	2 (0-4)	1.3 (1.0-1.7)	7 (5-10)	2.3 (1.8-3.0)
60-69	5	8	2 (0-6)		10 (7-16)	

Stroke

50-59	5	4	1 (1-2)	1.3 (1.1- 1.4)	1 (1-2)	1.3 (1.1- 1.4)
60-69	5	9	3 (1-4)		3 (1-4)	

Coronary heart disease (CHD)

	Age range (years)	Time (years)	Oestrogen [¶] O+P [¶]		Risk ratio (95% CI)	Additional cases per 1000 HRT users†	Risk ratio (95% CI)‡	
			Oestrogen [¶]	O+P [¶]				
	50-59	5	14	9	NS	0.6 (0.4-1.1)	NS	1.3 (0.8-2.1)
	60-69	5	31	18	NS	0.9 (0.7-1.2)	NS	1.0 (0.7-1.4)
	70-79	5	44	29	NS	1.1 (0.8-1.5)	15 (1-32)	1.5 (1.0-2.1)

Benefits**

Colorectal cancer

	Age range (years)	Time (years)	Oestrogen [¶] O+P [¶]		Risk ratio (95% CI)	Additional cases per 1000 HRT users†	Risk ratio (95% CI)‡	
			Oestrogen [¶]	O+P [¶]				
	50-59	5	6	3	NS	0.9 (0.7-1.1)	NS	0.9 (0.7-1.1)
	60-69	5	10	8	NS		NS	

Fracture of femur

	Age range (years)	Time (years)	Oestrogen [¶] O+P [¶]		Risk ratio (95% CI)	Additional cases per 1000 HRT users†	Risk ratio (95% CI)‡	
			Oestrogen [¶]	O+P [¶]				
	50-59	5	0.5	1.5	0	0.6 (0.4-0.9)	NS	0.7 (0.5-1.0)
	60-69	5	5.5	5.5	-2 (-3 to -1)		NS	

Table: **Risks and benefits of HRT**

Tibolone: benefit-risk balance

Keywords: Tibolone, Livial, hormone-replacement therapy, stroke, breast cancer, endometrial cancer, coronary heart disease, venous thromboembolism, interactions

Increased risk of stroke in older women should be taken into account in prescribing decisions

For further information, access the Public Assessment Report at http://www.mhra.gov.uk/home/idcplg?ldcService=SS_GET_PAGE&nodeId=230

1 Cummings SR. *BMJ* 2006; **332**: 667.

Tibolone (Livial) is a first-line treatment for menopausal symptoms and a second-line therapy for prevention of osteoporosis. The balance of benefits and risks for tibolone has been assessed after termination of a large randomised placebo-controlled trial (LIFT study) because of an increased risk of stroke in those assigned tibolone compared with those assigned placebo.¹

Benefit-risk balance in licensed indications

In younger women, the risk profile of tibolone is broadly similar to that for conventional combined hormone-replacement therapy (HRT). For women older than about 60 years, the risks associated with tibolone start to outweigh the benefits because of the increased risk of stroke.

Healthcare professionals should weigh the increased risk of stroke with tibolone against the increased risk of breast cancer with combined HRT for women with a uterus.

Stroke

The LIFT study identified a significantly (2.2-times) increased risk of stroke, mostly ischaemic, in tibolone users; risk increased from the first year of treatment. Baseline risk of stroke is strongly age-dependent, and so the absolute risk with tibolone increases with older age. Randomised controlled trials have identified an approximate 1.3-times increase in stroke risk for combined HRT.²

2 Wassertheil-Smoller S, et al. *JAMA* 2003; **289**: 2673–84.

Endometrial cancer

Most studies show an increased risk of having endometrial cancer diagnosed associated with use of tibolone. In the LIFT study, tibolone users (n=1746) were diagnosed with one additional case of endometrial hyperplasia and four additional cases of endometrial cancer compared with placebo users (n=1773) after 2.7 years of treatment. In observational studies, risk increased with longer duration of use. Break-through bleeding and spotting may occur during the first months of treatment with tibolone.

Healthcare professionals should refer women who bleed beyond 6 months of treatment, or after stopping treatment, for gynaecological investigation to exclude endometrial malignancy.

Breast cancer

There are limited clinical trial data for breast-cancer risk in healthy women. However, the LIBERATE study in women with previous breast cancer was stopped recently because it was unable to establish non-inferiority of tibolone compared with placebo.³

3 See http://www.organon.com/media/pres_s_releases/tibolone_study_to_close_a_head_of_schedule.asp

4 Million Women's Steering Committee.
Lancet 2003; **362**: 419–27.

For more information about the
General Practice Research Database,
see <http://www.gprd.com>

Why not share
this bulletin with
your colleagues?

The Million Women Study identified a significantly increased risk of having breast cancer diagnosed in tibolone users (relative risk [RR] 1.5 [95% CI 1.3–1.7]), which is comparable with that for oestrogen-only HRT (1.3 [1.2–1.4]) and significantly lower than that for combined HRT (2.0 [1.9–2.1]).⁴ Risk increased with longer duration of use and returned to baseline within a few years of stopping treatment. A study using the General Practice Research Database found no significant increase in risk. Unlike conventional HRT, tibolone has a limited effect on mammographic density.

Venous thromboembolism

The few data available do not suggest an increased risk of venous thromboembolism compared with combined HRT users or with non-users.

Coronary heart disease

No conclusions can be drawn from the available data. In view of the increased risk of stroke associated with tibolone, an increase in coronary events is biologically plausible. In studies, tibolone caused a marked dose-dependent decrease in HDL cholesterol (–22.4% after 2 years); total triglycerides and lipoprotein (a) levels were also reduced. A decrease in total cholesterol and VLDL cholesterol was not dose-dependent; levels of LDL cholesterol did not change. The clinical implication of these findings is not yet known.

Interactions

Tibolone may increase blood fibrinolytic activity and enhance the effect of anticoagulants such as warfarin. Limited data suggest that tibolone may interact with cytochrome P450 3A4 substrates such as midazolam.

Healthcare professionals should exercise caution in the simultaneous use of tibolone and anticoagulants such as warfarin, especially when starting or stopping tibolone.

Advice for healthcare professionals to consider before prescribing tibolone:

- Every woman's overall risk of stroke, breast cancer, and, in those with an intact uterus, endometrial cancer should be assessed carefully, taking into consideration any baseline risk factors, the increased risk due to tibolone use, and her therapeutic preferences

Desmopressin nasal spray: removal of nocturnal enuresis indication

Keywords: desmopressin, removal of indication, primary nocturnal enuresis, nasal spray

Nasal formulations of desmopressin are no longer indicated for primary nocturnal enuresis

Desmopressin is a synthetic analogue of vasopressin, and is indicated for treatment of primary nocturnal enuresis (PNE); nocturia associated with multiple sclerosis when other treatments have failed; and diagnosis and treatment of vasopressin-sensitive cranial diabetes insipidus; it is also indicated for establishment of renal concentration capacity.

Desmopressin is available as a nasal or oral formulation. The PNE indication has been removed from all desmopressin nasal spray products because of an increased risk of adverse effects compared with the oral formulation (which remains available for treatment of PNE).

Desmopressin produces a sustained decrease in urine output and a decrease in plasma osmolality, which can result in hyponatraemia and water intoxication in the presence of inappropriate fluid intake. About 15 cases of hyponatraemia per 100 000 patient-years of exposure for nasal desmopressin have been reported, compared with 5 cases per 100 000 patient-years for oral formulations. Most cases of hyponatraemia associated with use of nasal desmopressin occurred in patients younger than 18 years who were receiving treatment for PNE. There have also been reports of severe hyponatraemia in patients treated with nasal desmopressin for cranial diabetes insipidus. Most cases of hyponatraemia associated with oral desmopressin have been reported in elderly patients being treated for nocturia, but cases have also been reported in children.

Advice for healthcare professionals:

- Nasal formulations of desmopressin should not be used for treatment of PNE
- All patients with PNE should start oral desmopressin at the lowest recommended dose, which should be increased only if necessary to achieve control of symptoms
- Healthcare professionals and patients should follow closely the advice on fluid intake in the Summary of Product Characteristics and the Patient Information Leaflet to avoid hyponatraemia

Pabrinex: allergic reactions

Keywords: Pabrinex, vitamin B, vitamin C, thiamine, parenteral treatment, allergic reactions, risks and benefits, Wernicke-Korsakoff Syndrome

Rare occurrence of serious allergic reactions should not preclude use of parenteral thiamine in patients who need treatment by this route of administration

Pabrinex (B vitamins including thiamine) is indicated for rapid treatment of severe depletion or malabsorption of vitamins B and C, particularly in alcoholism, after acute infection occurring post-operatively or in psychiatric settings.

In 1989, the Committee on Safety of Medicines advised that the use of parenteral B vitamins should be restricted to patients in whom parenteral treatment was considered essential. This advice was based on reports of serious allergic reactions, including anaphylaxis, with use of Parentrovite products (which were then the high-dose B vitamin formulations licensed in the UK).

The Commission on Human Medicines has reviewed the safety of parenteral thiamine in the management of Wernicke-Korsakoff Syndrome (a neuropsychiatric condition that arises from thiamine deficiency). During 1975–91, 65 reports (2 fatal) of serious allergic reactions were received for Parentrovite, compared with 6 reports (1 fatal) for Pabrinex during 1992–2006. There have been no reports of serious allergic reactions with Pabrinex since 2001.

Has your
colleague seen
this bulletin?

Advice for healthcare professionals:

- Although potentially serious allergic adverse reactions might occur rarely during, or shortly after, parenteral administration of Pabrinex, such rare occurrence of serious allergic reactions should not preclude the use of parenteral thiamine in patients who need treatment by this route of administration—particularly those at risk of Wernicke-Korsakoff Syndrome, for whom treatment with thiamine is essential
- Intravenous administration should be by infusion over 30 min
- Treatment for anaphylaxis, including resuscitation facilities, should be available when parenteral thiamine is given

Corticosteroids: early psychiatric side-effects

Keywords: Systemic steroids, psychiatric, class effect, patients, carers, benefits, Patient Information Leaflet, steroid card

Risk of early psychiatric side-effects is one of several important safety issues for healthcare professionals to discuss with patients and carers. Patients or carers should seek urgent medical advice in the event of any worrying symptoms

Corticosteroids are used in varying doses to treat a wide range of diseases. Psychiatric side-effects can occur with all systemic steroids. A recent case report of the suicide of a 16-year-old has highlighted the need to consider these common reactions and warn patients and their carers about the risks.

Types of reaction

A wide range of psychiatric reactions have been reported in association with corticosteroids, including: affective disorders (eg, irritable, euphoric, depressed, and labile mood, and suicidal thoughts); psychotic reactions (eg, mania, delusions, hallucinations, and aggravation of schizophrenia); behavioural disturbances; irritability; anxiety; sleep disturbances; and cognitive dysfunction (including confusion and amnesia).

Onset, severity, frequency, and risk factors

Psychiatric symptoms typically emerge a few days or weeks after the start of treatment. Risks may be higher with high doses compared with low doses, although there is no clear relation between dose and type, severity, or duration of reactions. Most patients recover from these reactions after dose reduction or withdrawal, although specific treatment might be necessary.

Reactions can occur in adults and children. In adults, the frequency of severe psychiatric reactions might be as high as 5–6%.¹ Psychiatric side-effects have also been reported on withdrawal of corticosteroids. Patients with previous history or close family history of severe affective disorders (especially steroid psychosis) should be treated with particular care; however, there is no firm evidence of an increased risk in these patients compared with others.

Important information for patients and carers

- All patients (or their carers) should be informed of the important benefits of steroid treatment, and should be warned of the most important safety issues associated with acute and chronic use (see box below)
- All patients (or their carers) who receive systemic steroids should receive a Patient Information Leaflet
- All patients should seek urgent medical advice in the event of worrying symptoms (eg, suicidal thoughts) or illness while taking systemic steroids
- Patients who take systemic steroids for more than 3 weeks or high-dose inhaled steroids should not stop treatment abruptly, and should be given a steroid card by their doctor or pharmacist^{2,3}

A list of questions and answers for patients on the safety of corticosteroids is available on the MHRA website.

1 Lewis DA, Smith RE. *J Affect Disord* 1983; **5**: 319–32.

2 *Current Problems in Pharmacovigilance* 1998; **24**: 5–7.

http://www.mhra.gov.uk/home/idcplg?ldcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON007473&ssTargetNodId=368

3 *Current Problems in Pharmacovigilance* 2006; **31**: 5.

http://www.mhra.gov.uk/home/idcplg?ldcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2023859&ssTargetNodId=368

For a list of questions and answers for corticosteroids see <http://www.mhra.gov.uk/mhra/steroids>

Key safety issues to discuss with patients given systemic steroids and their carers

- **Endocrine:** adrenal suppression, Cushing’s syndrome
- **Eye:** cataracts, glaucoma, and papilloedema
- **Gastrointestinal:** ulceration, pancreatitis, candidiasis
- **Immune:** increased susceptibility to infections—especially chickenpox
- **Musculoskeletal:** myopathy, osteoporosis, fractures, growth suppression
- **Neurological:** aggravation of epilepsy
- **Psychiatric:** psychosis; affective (eg, risk of suicide), behavioural, and cognitive disorders

Yellow Card scheme update

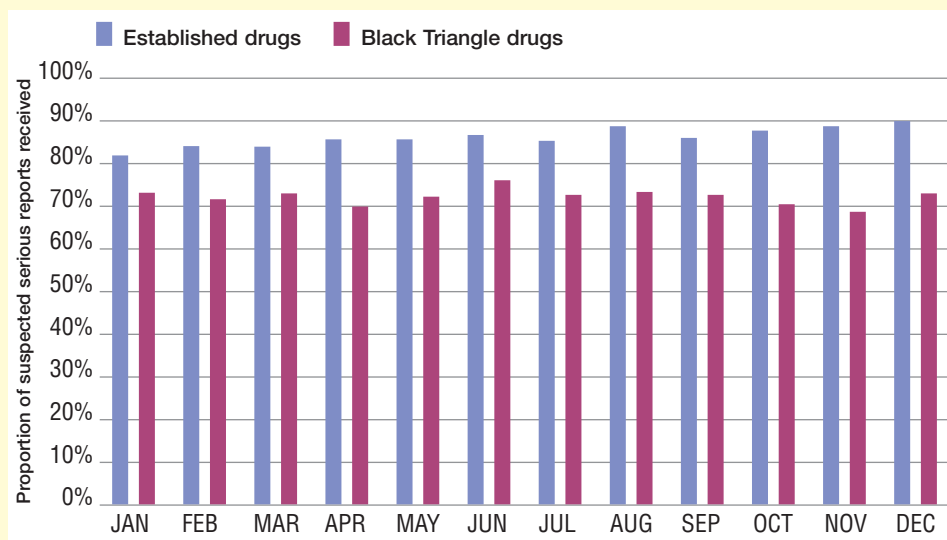
The Yellow Card scheme collects information from healthcare professionals and patients on suspected adverse drug reactions.

We encourage healthcare professionals to send reports for:

- All adverse drug reactions associated with black triangle ▼ drugs and vaccines (ie, those new to the market and monitored intensively)
- All adverse drug reactions in children associated with a drug or vaccine
- All serious reactions associated with established drugs and vaccines
- Suspected delayed drug effects; congenital abnormalities; and adverse drug reactions associated with herbal remedies

We are grateful to all healthcare professionals who send us Yellow Cards. Please continue to send us Yellow Cards, in line with the guidelines above.

The figure below shows the proportion of reports for established drugs and black triangle drugs that are classed as serious by month of reporting for the 4-year period 2002–06.



For further information, see <http://www.yellowcard.gov.uk>.

For information on black triangle drugs see http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAG E&nodeId=748

For information on the definition of “serious”, see http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAG E&nodeId=752

For further information on delayed drug effects, congenital abnormalities and herbal remedies, see http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAG E&nodeId=751

For information on what to include in a Yellow Card report, see http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAG E&nodeId=753

Hot topic

Duloxetine: marketed as Cymbalta ▼ and Yentreve ▼ for different disorders

Duloxetine is a prescription-only medicine that is indicated for treatment of three different disorders—major depressive disorder, diabetic neuropathy, and stress urinary incontinence. For treatment of major depressive disorder and diabetic neuropathy, duloxetine is marketed as Cymbalta ▼; for treatment of stress urinary incontinence, duloxetine is marketed as Yentreve ▼.

Cases of suicidal ideation and suicidal behaviour have been reported during treatment with duloxetine or early on after stopping treatment. Patients and caregivers should monitor and report to their doctor any distressing thoughts or feelings, signs of depression, suicidal behaviour or ideation, or thoughts of self-harm if they occur at any time during or after treatment with Cymbalta or Yentreve; healthcare professionals should encourage patients to report any of these thoughts, feelings, or signs during treatment with Cymbalta or Yentreve.

- Cymbalta and Yentreve should be prescribed for their correct intended use, and should not be used together
- The benefit to the patient of taking Cymbalta for diabetic neuropathy should be assessed by a doctor at least every 3 months
- The benefit of Yentreve for patients with stress urinary incontinence should be assessed regularly
- Cymbalta or Yentreve should not be prescribed to patients who have: liver disease leading to impaired liver function; severe kidney impairment; uncontrolled hypertension
- Cymbalta or Yentreve should not be prescribed to patients who are also taking: non-selective, irreversible monoamine oxidase inhibitors for depression such as phenelzine (Nardil), isocarboxazid, or trancyclopropmine; fluvoxamine for depression or obsessive compulsive disorder; or the antibiotic ciprofloxacin. Cymbalta should be used with caution alongside other antidepressants or St John's Wort. The use of Yentreve in combination with antidepressants is not recommended
- Patients should avoid abrupt withdrawal of treatment from Cymbalta or Yentreve. Healthcare professionals should prescribe gradually reduced doses over at least 1–2 weeks to minimise withdrawal reactions. If a patient has intolerable symptoms after decreasing or stopping Cymbalta or Yentreve, the drug may be re-prescribed or the dose increased; any subsequent reductions in dose may be done more gradually

See
[http://www.mhra.gov.uk/mhra/
duloxetine](http://www.mhra.gov.uk/mhra/duloxetine)

Further information about duloxetine is available on the MHRA website.

Stop press

Safety information sent to healthcare professionals by Marketing Authorisation Holders is published and updated monthly on our website. See <http://www.mhra.gov.uk/mhra/HealthcareProfessionalLetters>

For further information about the recall of nelfinavir, see *Drug Safety Update 2007*; 1: 10. See <http://mhra.gov.uk/mhra/drugsafetyupdate>

See <http://www.mhra.gov.uk/mhra/SafetyWarningsAndMessagesForMedicines>

Recent letters to healthcare professionals

In July, 2007, letters were sent to healthcare professionals to inform them of updated safety information for **piroxicam** (Feldene, new prescribing restrictions as second-line treatment for osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis to be initiated only by specialists in the management of arthritic disorders), and for **nelfinavir** (Viracept, establishment of patient registries to follow-up patients who have potentially been exposed to a genotoxic contaminant).

Latest safety information

For the latest information on the safety of **lumiracoxib** (Prexige ▼), see our website.

To download the report Medicines & Medical Devices Regulation: What you need to know, see http://www.mhra.gov.uk/home/idcplg?ldcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2031733&ssTargetNodeid=387

Other information from the MHRA

New publication

The MHRA has published an introductory guide to how it regulates medicines and medical devices in the UK. The guide explains how we license and authorise medicines and medical devices, how we monitor their safety, and how we influence policy.

For further information on the Inspectorate see http://www.mhra.gov.uk/home/idcplg?ldcService=SS_GET_PAGE&nodeid=135

Read the latest edition of MAIL, our updating service for medicines, at http://www.mhra.gov.uk/home/idcplg?ldcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2031825&ssTargetNodeid=380

Inspections

The MHRA's Inspection and Standards division has a range of inspectors who specialise in different inspections to ensure good practice in the medicines industry with regard to pharmacovigilance, clinical practice, manufacturing, distribution, and laboratory practice. The division inspects research, development, and quality-control laboratories; clinical trials; manufacturers; wholesalers; and pharmacovigilance systems. Some inspections are done overseas and on behalf of the European Medicines Agency.

Adverse findings during inspection may lead to further inspections in other areas of a company's quality system. Inspectors ensure that appropriate legislation and guidance are fulfilled, and that relevant facilities are up to standard.

See <http://www.mhra.gov.uk/mhra/Advertising>

Advertising

The MHRA's Advertising Standards Unit scrutinises promotional material about medicines. Anyone who has concerns about misleading advertising can contact us through our website. We are particularly keen to receive complaints from healthcare professionals. In July, 2007, the Advertising Standards Agency fully upheld complaints made by the MHRA about inaccurate and misleading medicinal claims made by the Everwell Chinese Medicine Centre (Kent) about traditional Chinese medicines. We advise consumers to be wary and vigilant about clinics that make extravagant claims about its herbal medicines.

Read more about the Commission on Human Medicines, including summaries of minutes from meetings, at <http://www.mhra.gov.uk/mhra/CommissiononHumanMedicines>

Copies of this bulletin can be downloaded at <http://www.mhra.gov.uk/mhra/drugsafetyupdate>