Drug Safety Update

MHRA

Latest advice for all medicines users

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

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1 year has passed since the introduction of the vital UK immunisation programme against human papillomavirus (HPV) with Cervarix. As with all vaccines and medicines, MHRA and CHM are responsible for continually monitoring the safety of Cervarix in the UK. This month, we present a safety overview of Cervarix, based on information we have received from you via the Yellow Card Scheme (p 5). This Scheme is vital to our safety monitoring, so please continue to report any suspected adverse reactions to us via www.yellowcard.gov.uk. Remember that patients and the general public can also report via this website. Further information on HPV vaccination is available on our website at www.mhra.gov.uk/HPVvaccine

A Hot topic this month looks at the clinically significant interactions between smoking, or smoking cessation, and commonly used medicines. Smoking induces the drug-metabolising enzyme CYP1A2 and thus in patients who smoke, or who are cutting down or stopping smoking (with or without the aid of drug treatment), the doses of any concomitant medication metabolised by CYP1A2 may need to be adjusted accordingly. Read more about how smoking status may be relevant to prescribing and the risk of drug-related side effects on p 9.

Also this month, we update our advice from November 2007 on ceftriaxone. This broad-spectrum cephalosporin antibiotic should not be given simultaneously with calcium-containing solutions (other than total parenteral nutrition solutions) for intravenous administration because of a risk of calcium precipitation. Furthermore, ceftriaxone is contraindicated in newborns up to age 28 days who need intravenous treatment with any calcium-containing solution. Further advice is on p 2.

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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 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

Ceftriaxone (Rocephin): incompatibility with calcium-containing solutions—updated advice

Keywords: ceftriaxone, Rocephin, Ringer's, Hartmann's, total parenteral nutrition (TPN) solutions, incompatibility, precipitation, calcium, neonate, newborns

Ceftriaxone should **not** be given simultaneously with calcium-containing solutions (other than total parenteral nutrition solutions) for intravenous administration because of a risk of calcium precipitation. Ceftriaxone is contraindicated in newborns up to age 28 days who need intravenous treatment with any calcium-containing solution. Calcium and ceftriaxone may be infused sequentially in patients aged 28 days or older provided that either a) the infusion line is rinsed or flushed between solutions, or b) the infusions are given via different infusion lines at different sites

Ceftriaxone (Rocephin) is a broad-spectrum cephalosporin antibiotic that is used to treat infections known or likely to be due to one or more susceptible micro-organisms and when parenteral therapy is needed. Ceftriaxone can be given by deep intramuscular injection, slow intravenous injection, or by slow intravenous infusion after reconstitution of the solution.

Ceftriaxone and calcium precipitation

We have previously reminded healthcare professionals that ceftriaxone should not be mixed or simultaneously infused with calcium-containing solutions such as Hartmann's or Ringer's because of a risk of precipitation.

See Drug Safety Update November 2007, p 5; www.mhra.gov.uk/mhra/drugsafetyupdate

We also advised that ceftriaxone is contraindicated in newborns who need calcium treatment because of a risk of precipitation of ceftriaxone–calcium salt.

Review of available data

A review of the available data suggests that newborns (up to age 28 days) are at greater risk of calcium–ceftriaxone precipitation than older patients, particularly if they are premature or have impaired bilirubin binding.

The risk of calcium–ceftriaxone precipitation in adults is likely to be low; however, as a precaution, ceftriaxone and calcium should **not** be administered simultaneously by the intravenous route. However, they may be given sequentially in patients age 28 days or older if the infusion line is rinsed or flushed between solutions, or the infusions are given via different infusion lines at different sites.

Some total parenteral nutrition (TPN) solutions contain similar levels of calcium to that in saline solutions such as Ringer's or Hartmann's, and may present a similar degree of risk.

Latest advice for healthcare professionals:

✘ • Ceftriaxone is contraindicated in:
  – premature newborns up to a corrected age of 41 weeks (weeks of gestation+weeks of life)
  – full-term newborns up to age 28 days who:
    – need treatment with calcium-containing solutions (including TPN solutions), because of a risk of precipitation of ceftriaxone–calcium salt
    – have jaundice or who are hypoalbuminaemic or acidotic, because these are conditions in which bilirubin binding is likely to be impaired

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✘ • Simultaneous infusion: for all patients, ceftriaxone must not be mixed with calcium-containing intravenous solutions, and must **not** be given simultaneously with calcium-containing solutions—even via different infusion lines

✔ • Sequential infusion: calcium and ceftriaxone may be infused sequentially in patients aged 28 days or older provided that either a) the infusion line is rinsed or flushed between solutions, or b) the infusions are given via different infusion lines at different sites

• In patients requiring continuous nutrition with calcium-containing TPN solutions, healthcare professionals may wish to consider using alternative antibacterial treatments which do not carry a similar risk of precipitation. If there is no alternative to giving ceftriaxone with TPN solutions, then administration can be simultaneous provided they are given via different infusion lines at different sites

High-dose cyproterone acetate: potential risk of (multiple) meningiomas

Keywords: Cyproterone acetate, meningiomas, prostate cancer, libido control

Patients with existing meningioma or a history of meningioma must not be prescribed high-dose (≥25 mg per day) cyproterone acetate. This advice does **not** apply to low-dose cyproterone acetate products such as co-cyprindiol (Dianette)

Has your colleague seen this bulletin?

Cyproterone acetate-containing products

Cyproterone acetate is a derivative of progesterone, and has progestagenic, antiandrogenic, and antigonadotrophic effects. High-dose preparations available in the UK include Cyprostat-50 and Cyprostat-100, which are indicated for use in the treatment of prostate cancer (dose 50–300 mg per day). Cyproterone acetate is also available as Androcur-50, which is indicated for the control of libido in men with severe hypersexuality or sexual deviation (or both). In some EU countries, Androcur-50 is used for the treatment of androgenisation in women. Although this is not a licensed indication in the UK, there is some evidence that high-dose cyproterone acetate is being used for this purpose here.

Lower-dose cyproterone acetate (ie, 2 mg) is available for use in women as co-cyprindiol (Dianette) in combination with 35 micrograms ethinylestradiol for the treatment of severe acne that is refractory to prolonged antibiotic therapy, and for moderately severe hirsutism.

Meningiomas

Meningiomas are the most common intracranial tumours, with an annual incidence of six per 100 000 in the general population. Multiple meningiomas account for approximately 1–10% of all cases. Though histologically benign, they can have serious consequences. The potential role of sex hormones in the development of meningiomas has been postulated: approximately 70% of meningiomas express progesterone receptors and about 30% express oestrogen receptors.[1]

1 Blitshteyn S, et al. *J Clin Oncol* 2008; **26**: 279–82.

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The occurrence of (multiple) meningiomas has been reported in association with longer-term use (years) of cyproterone acetate at doses of 25 mg/day or higher.

Summary of evidence

Up to September 2009, 36 cases of meningioma, of which 19 described multiple meningioma, have been reported worldwide in association with high-dose cyproterone acetate. Nine cases were discussed in a published case series,[2] and 27 cases are unpublished case reports. Of the 36 cases, 32 occurred in women and four in men. Duration of treatment with cyproterone acetate ranged from 4 years to 27 years, and in all but one case it was prescribed at doses higher than 25 mg per day. 31 of the cases were from France (which compared with other countries has extensive use of high-dose cyproterone acetate). None of the reported cases had a fatal outcome.

A retrospective cohort study with nested case-control analysis is currently being done by the brand-leader marketing authorisation holder using data from The Health Improvement Network database (THIN) in the UK, to further investigate the association between cyproterone acetate and meningioma. The main study objectives will be to estimate the incidence of meningioma in the general population and among users of cyproterone acetate, and to examine whether there is a dose-response relationship and a duration-response relationship between use of cyproterone acetate and meningioma.

Product information for all products in the UK that contain high-dose cyproterone acetate will be updated in line with the advice below.

Advice for healthcare professionals:

- Patients with existing meningioma or a history of meningioma must not be prescribed cyproterone acetate at doses of 25 mg per day or higher (ie, should not receive Cyprostat-50, Cyprostat-100, or Androcur-50)
- This advice does **not** apply to medicines that contain low-dose cyproterone acetate such as co-cyprindiol (Dianette)

2 Froelich S, et al. *Endocrine Abstracts* (Proceedings of the 10th European Congress of Endocrinology; Berlin, Germany) 2008; **16**: 158. http://www.endocrine-abstracts.org/ea/0016/ea0016p158.htm (accessed Aug 26, 2009).

Yellow Card Scheme update

The Yellow Card Scheme collects information on suspected adverse drug reactions in the UK. See www.yellowcard.gov.uk

Human papillomavirus (HPV) immunisation programme—first year safety review

The human papillomavirus (HPV) immunisation programme is now entering its second year. The programme has so far been a success and the latest uptake levels continue to be very encouraging. At least 1.4 million doses of Cervarix HPV vaccine have now been administered across the UK. More information on the programme can be found at www.immunisation.nhs.uk.

This level of exposure in the UK is an important milestone in understanding the overall safety profile of the vaccine during routine use. This article summarises the safety experience to date.

- The total number and nature of suspected side effects reported via the Yellow Card Scheme during the first year of the Cervarix vaccination programme has been very much as expected
- Most reports have related to the signs and symptoms of recognised side effects, which are generally not serious
- No new risks have been identified, and the balance of risks and benefits remains positive
- As with all vaccines, the MHRA and Commission on Human Medicines (CHM) will continue to monitor closely the safety of Cervarix during continued use in the UK

MHRA pharmacovigilance strategy

The MHRA continuously monitors the safety of all vaccines and medicines used in the UK, including Cervarix HPV vaccine (as well as Gardasil HPV vaccine, which is not used in the routine immunisation programme).

We receive reports of suspected side effects via the Yellow Card Scheme. It is important to bear in mind that a report of a suspected adverse reaction does not necessarily mean that it has been caused by Cervarix. Reports may represent true side effects, or they may be due to underlying illness and therefore purely co-incidental events that would have occurred anyway in the absence of vaccination.

As part of the Cervarix pharmacovigilance strategy, at the start of the immunisation programme we wrote to healthcare professionals involved to encourage use of the Yellow Card Scheme to report suspected side effects. The Scheme is also open to members of the public. We review all new reports of suspected side effects on a daily basis, using an epidemiological approach to detect potential safety signals. Our ongoing analysis of the safety of Cervarix is published every week at www.mhra.gov.uk/hpvvaccine.

Cervarix: current safety profile

As at the end of July 2009, the MHRA had received 2195 Yellow Cards, including 4830 adverse-reaction terms, in association with Cervarix (including reports in which the brand of HPV vaccine was not stated by the reporter). Most Yellow Card reports have been submitted by nurses (mainly school nurses).

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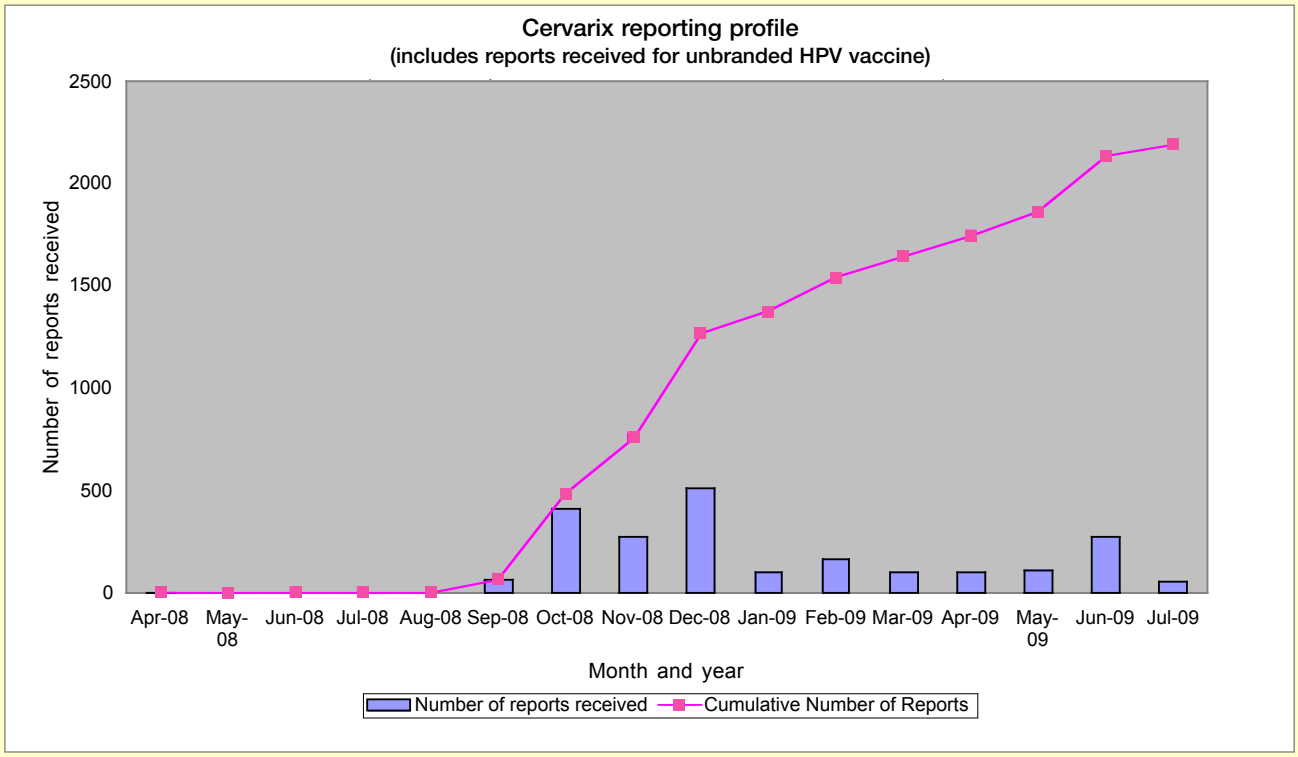
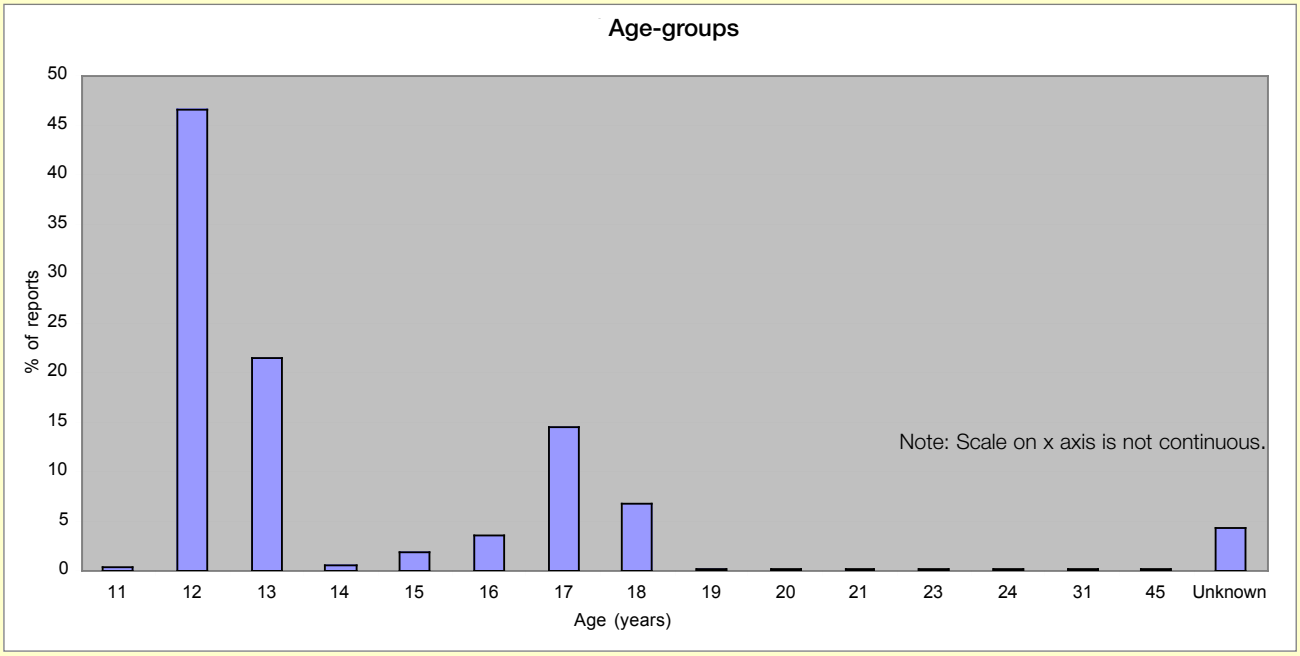
Number of reports received between April 2008 and July 2009:



Range of Yellow Card reports received based on patient age:



As expected, most reports were for girls age 12–13 years and 17–18 years—the age-groups targeted in the first year of the immunisation programme.

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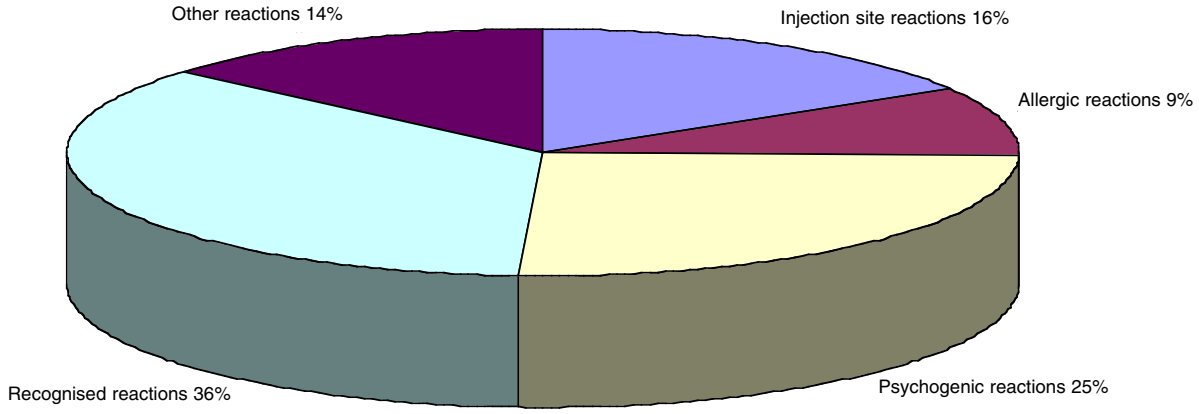
Type of adverse reactions reported to the Yellow Card Scheme:

Proportion and category of adverse reactions reported with Cervarix vaccine and HPV (unbranded) vaccine



Psychogenic events include vasovagal syncope, faints, panic attacks, and associated symptoms. These can occur with any injection procedure, not only vaccination, and can be common in adolescents. Such events can be associated with a wide range of temporary signs and symptoms, including: loss of consciousness; vision disturbance; injury; limb jerking (often misinterpreted as a seizure or convulsion); limb numbness or tingling; and difficulty in breathing or hyperventilation. These are due to fear or anticipation of the needle injection and are not side effects of Cervarix vaccine as such. More information on the specific adverse reactions reported can be found at www.mhra.gov.uk/hpvvaccine.

The ten most commonly reported suspected adverse reactions up to the end of July, 2009 were:

Suspected adverse reaction	Number of reports	Suspected adverse reaction	Number of reports
1. Dizziness	468	6. Vomiting	178
2. Headache	433	7. Malaise	161
3. Nausea	422	8. Fatigue	133
4. Pain in extremity	248	9. Pyrexia	106
5. Syncope	199	10. Rash	96

Potential safety issues assessed

Chronic Fatigue Syndrome and associated conditions

Based on case reports of chronic fatigue syndrome (CFS) and associated conditions, the MHRA sought the advice of CHM on whether the available evidence provided any indication that Cervarix may cause these conditions.

CFS is a fairly common condition that occurs naturally among the population of girls vaccinated. CHM noted that as more than 1 million doses of Cervarix have been given in the UK, at least 60 cases of CFS would have been expected already by chance alone. Accounting for various levels of possible under-reporting to the Yellow Card Scheme, the 13 reports of possible chronic-fatigue-like symptoms (including cases reported in the UK media) do not indicate that Cervarix is causing any excess of CFS cases.

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CHM also noted that there are insufficient clinical details to determine if any of the reported cases met the case definition of CFS as defined by the National Institute for Health and Clinical Excellence, and there was a lack of consistency in the clinical pattern between cases. Even if such cases were eventually confirmed to be CFS, CHM advised that the evidence does not support a causal link with Cervarix vaccine because many more cases would have been expected to occur by chance among the number of girls immunised so far. This issue will remain under review by the MHRA.

Guillain-Barré syndrome and facial palsy

One case of Guillain-Barré syndrome and one case of facial palsy have been reported via the Yellow Card Scheme. Our analysis of the reporting rate of such conditions compared with the expected incidence among adolescent girls indicates that the vaccine is not associated with a risk of these conditions.

Summary

The number and nature of suspected adverse reactions received so far is very much in line with what we expected to receive at this time. CHM reviewed these data on Sept 18, 2009 and agreed that following substantial usage no new or serious risks have been identified during use of Cervarix in the UK, and that the balance of benefits and risks remains positive. As with all vaccines, the MHRA and CHM will continue to closely monitor the safety of Cervarix during continued use in the UK.

Have you reported a Yellow Card for the HPV vaccine?

As the start of the second year of the Cervarix immunisation programme begins, it is essential that all three doses are given to ensure protection. Thank you to those who have sent us Yellow Cards for Cervarix. Please continue to help us monitor the safety of Cervarix by reporting any suspected adverse reactions associated with the vaccine via the Yellow Card Scheme, either online at www.yellowcard.gov.uk or by post (paper Yellow Cards are available at the back of the British National Formulary or call 0800 731 6789). Please also remind vaccinees and their carers that they too can also report suspected side effects via the Yellow Card Scheme.

Information for vaccinees and parents

In its August edition of Vaccine Update (www.immunisation.nhs.uk), the Department of Health reminded healthcare professionals of the importance of fully informing vaccinees/their carers about their immunisations and possible side effects. It stressed the need to provide verbal or written information, which may take the form of provision and discussion of the patient information leaflet (PIL). The MHRA fully endorses this advice. PILs are provided in the Cervarix vaccine packs and can also be viewed/downloaded via the electronic Medicines Compendium (http://emc.medicines.org.uk).

Hot topic

This Hot topic discusses how a patient's smoking status may affect prescribing decisions

Smoking and smoking cessation: clinically significant interactions with commonly used medicines

Pharmacokinetic interactions

Polycyclic aromatic hydrocarbons (PAHs) found in tobacco smoke are potent inducers of the hepatic cytochrome P450 (CYP) isoforms 1A1, 1A2, and possibly 2E1. Of these, 1A2 is the most important. Enzyme induction results in increased metabolism of substrates. Thus larger doses of CYP1A2 substrates may be required to ensure efficacy in people who smoke, and a reduction in dose may be needed during smoking cessation to prevent side effects.

Many commonly used medicines are substrates for CYP1A2: theophylline; fluvoxamine; caffeine; coumarins, including warfarin; and the antipsychotics clozapine and olanzapine. However, not all possible drug-smoking interactions are clinically significant. Important factors that determine the clinical significance of an interaction in smokers are:

- The extent to which the medicine is metabolised by CYP1A2—ie, the fractional clearance. The interaction will be most significant when CYP1A2 is the main elimination pathway
- The therapeutic index of the medicine metabolised for CYP1A2. For example, for a narrow therapeutic index drug such as theophylline, small changes in drug concentration may have significant clinical effects

It is also important to remember that it takes about 1 week for the effect of the induction of CYP1A2 to wear off after smoking cessation, and thus dose adjustment is not usually necessary in situations where there is temporary smoking cessation (eg, during acute hospital stay).

Further information on the most clinically significant pharmacokinetic drug interactions with smoking can be found in: Kroon LA. Drug interactions with smoking. *Am J Health Syst Pharm* 2007; **64**: 1917–21. See also Baxter K. Stockleys Drug Interactions (Pharmaceutical Press, 2007). www.medicinescomplete.com/mc/stockley/current/

Pharmacodynamic interactions

Pharmacodynamic interactions between medicines and smoking or smoking cessation are attributable to the effects of tobacco smoke, including nicotine. The most clinically significant pharmacodynamic interactions with smoking include: hormonal contraceptives (increased risk of cardiovascular disease); inhaled corticosteroids (efficacy may be reduced in smokers with asthma); and beta-blockers (nicotine activation of sympathetic nervous system may counteract effect).

Furthermore, stopping smoking, with or without the aid of drug treatment, may be associated with psychiatric symptoms, and stopping smoking may also exacerbate an underlying psychiatric condition.

Advice for healthcare professionals:

Clear guidelines for clinical practice are not available. We would thus suggest the following general approach should be taken:

- On starting CYP1A2 substrates:
  - Obtain smoking status
  - Determine clinical significance of any potential interaction
  - Monitor efficacy and side effects
  - Adjust dose if necessary
  - Monitor smoking status and advise patients to seek advice from doctor if smoking status is to change

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- During smoking cessation:
  - Find out what medicines the patient is taking
  - Determine clinical significance of any potential interaction
  - Monitor for side effects
  - Adjust dose if necessary

The most important medicines to consider in those who smoke, or who are trying to quit, include theophylline, olanzapine, clozapine, caffeine, and warfarin.

Remember that you can report suspected interactions on a Yellow Card at www.yellowcard.gov.uk

Hot topic

Aspirin: not licensed for primary prevention of thrombotic vascular disease

Two recent studies have looked at the use of low-dose aspirin in the prevention of heart attacks and strokes in people without a history of vascular disease—ie, primary prevention. Both studies found that the risk of having a major bleed—gastrointestinal bleeding is a known adverse effect of aspirin—outweighed any vascular benefit.

In the UK, low-dose aspirin is licensed for prevention of thrombotic cerebrovascular or cardiovascular disease only in those who already have vascular disease—ie, secondary prevention. Although aspirin is used in primary prevention, this is not a licensed indication.

Recent evidence supporting the current licensed indications for aspirin

AAA study

The Aspirin for Asymptomatic Atherosclerosis trialists at the University of Edinburgh recently reported the outcome of their randomised study at the European Society of Cardiology Congress in Barcelona, Spain.

Access the abstract, session number 175–76, at http://www.escardio.org/congresses/esc-2009/congress-reports/Pages/706001-706002-fowkes-patrono.aspx (accessed Sept 7, 2009).

Between 1998 and 2001, 3350 people in Scotland were recruited who were asymptomatic but at high risk of vascular disease. Participants were randomly assigned aspirin (100 mg/day) or matching placebo, with a mean follow-up of 8·2 years. The primary endpoint was a composite of initial coronary event or stroke or revascularisation (non-fatal or fatal).

For the primary endpoint, no significant difference was found between those allocated aspirin or placebo (181 events *vs* 176 events; hazard ratio 1·03 [95% CI 0·84–1·27]). An initial event of major haemorrhage requiring hospital admission occurred in 34 (2%) patients in the aspirin group and in 20 (1·2%) in the placebo group (hazard ratio 1·71 [0·99–2·97]). This study therefore found no benefit of aspirin use and an increased risk of serious bleeding in asymptomatic individuals.

ATT collaboration

The Antithrombotic Trialists Collaboration at the University of Oxford did a meta-analysis to investigate the effect of long-term, low-dose aspirin on the prevention of serious vascular events (ie, heart attack, stroke, or vascular death) and the risk of major bleeds in primary and secondary prevention.

See *Lancet* 2009; **373**: 1821–22

The analysis looked at six primary-prevention trials (95 000 people at low average risk) and 16 secondary-prevention trials (17 000 people at high average risk), which all compared aspirin with a control.

In the primary-prevention trials, aspirin reduced serious vascular events by 12% per year compared with no aspirin (0·51% *vs* 0·57%; p<0·0001), but significantly increased major bleeds (although they remained uncommon: 0·1% per year with aspirin *vs* 0·07% per year without aspirin; p<0·0001). In the secondary-prevention trials, aspirin reduced serious vascular events by 22% per year compared with no aspirin (6·7% *vs* 8·2%; p<0·0001) and had a similar effect on major bleeds.

The results of this analysis suggest that aspirin has substantial overall benefit in secondary prevention because it reduces serious cardiovascular events by much more than it increases the risk of major bleeds. However, in primary prevention the absolute risk of a serious vascular event is far lower than in secondary prevention and any vascular benefit of aspirin is likely to be at least partly offset by the small increase in serious bleeding events.

Advice for healthcare professionals:

- The results of these recent studies lend support to the licensed indications for aspirin in secondary prevention of vascular events only
- Aspirin is not licensed for the primary prevention of vascular events. If aspirin is used in primary prevention, the balance of benefits and risks should be considered for each individual, particularly the presence of risk factors for vascular disease (including conditions such as diabetes) and the risk of gastrointestinal bleeding

For further information on prescribers' responsibilities regarding use of unlicensed medicines or off-label use of medicines, see Drug Safety Update April 2009, p 6; www.mhra.gov.uk/mhra/drugsafetyupdate

Further information from the National Prescribing Centre on this topic is available at http://www.npci.org.uk/blog/?p=359

Stop press

Varenicline and suicidal behaviour: cohort study provides some reassurance

A study has recently been published which used the General Practice Research Database to determine whether varenicline ▼ may be associated with an increased risk of suicide and suicidal behaviour compared with bupropion or nicotine-replacement therapy (NRT). This nested cohort study analysed 80 660 people prescribed a new course of smoking-cessation product between Sept 1, 2006 and May 31, 2008.

See Gunnell D, et al. *BMJ* 2009; **339**: b3805.

The study found no clear evidence that varenicline was associated with an increased risk of fatal or non-fatal self-harm, although a two-fold increased risk cannot be ruled out on the basis of the upper 95% CI. Compared with NRT, the hazard ratio for self-harm in people prescribed varenicline was 1·12 (95% CI 0·67–1·88), and was 1·17 (0·59–2·32) for those prescribed bupropion. There was no evidence that varenicline was associated with increased risk of depression (0·88 [0·77–1·00]) or suicidal thoughts (1·43 [0·53–3·85]).

For the latest safety information on varenicline, see Drug Safety Update November 2008, p 2; www.mhra.gov.uk/mhra/drugsafetyupdate

As with all medicines, the MHRA will continue to closely monitor the safety of varenicline. Please remember that you can report any suspected adverse reactions to varenicline on a Yellow Card at www.yellowcard.gov.uk

Other information from the MHRA

Patient Information Leaflet of the month:

Patient information leaflets (PILs) are improving in quality as a result of new legal obligations on manufacturers to test the documents with potential patients. Testing makes sure that the presentation of the information enables patients to find and understand key messages for safe use about the medicine within the PIL and thereby enables them to use the medicine safely and effectively. To promote this new initiative, we are publishing a series of examples of best practice on our website. The latest in the series is for some medicines used in the treatment of tuberculosis that contain **isoniazid**, **rifabutin**, or **rifampicin**. The leaflets include information on the disease being treated, which in testing was found helpful.

Examples of leaflets in this feature can be found at:
http://www.mhra.gov.uk/Howweregulate/Medicines/Labelspatientinformationleafletsandpackaging/Patientinformationleaflet(PIL)ofthemonth/index.htm

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

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