Drug Safety Update

MHRA

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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Contents

This September, routine immunisation for human papillomavirus (HPV) will begin across the UK for girls age 12–13 years (see http://www.immunisation.nhs.uk/Vaccines/HPV/Resources). The safety and efficacy of the vaccine—Cervarix—was extensively studied in clinical trials before licensing. However, as with all vaccines and medicines used in the UK, it is important that the MHRA continues to monitor the safety of this important vaccine during routine use. You can help us by reporting via the Yellow Card Scheme adverse reactions that you suspect may have been caused by HPV vaccine (see www.yellowcard.gov.uk). If you have a role in delivering the HPV immunisation programme, please read our guidance on p 4 and p 5.

Fentanyl patches are an effective treatment for malignant and non-malignant chronic intractable pain. However, they must be used correctly and with care. We have received reports of life-threatening adverse reactions and death after fentanyl overdose possibly related to dosing errors, accidental exposure, and patch exposure to a heat source (which may increase drug absorption). Please read our information for healthcare professionals, patients, and caregivers on p 3 to help minimise the risks associated with these patches.

Remember you can tell us about suspected adverse drug reactions by completing a Yellow Card at www.yellowcard.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

Fentanyl patches: serious and fatal overdose from dosing errors, accidental exposure, and inappropriate use

Keywords: fentanyl patches, opioid analgesic, chronic pain, overdose, death, dosing errors, accidental exposure

We have received reports of unintentional overdose of fentanyl due to dosing errors, accidental exposure, and exposure of the patch to a heat source. Fentanyl is a potent opioid analgesic and should be used only in patients who have previously tolerated opioids

For further information about controlled drugs and the Misuse of Drugs Regulations see http://www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Prescriptions/ControlledDrugs/index.htm

Fentanyl patches are licensed for the management of malignant and non-malignant chronic intractable pain. Fentanyl is a controlled drug in the UK and is subject to schedule 2 of the Misuse of Drugs Regulations. Common brands include Durogesic DTrans, Durogesic, Matrifen ▼, and Tilofyl.

Reports of life-threatening adverse reactions and death

We have received spontaneous reports from healthcare professionals, patients, and carers of life-threatening adverse reactions and death after fentanyl overdose in people who were using the patches to control malignant and non-malignant pain.

Factors identified as possibly related to unintentional overdose include dosing errors (by healthcare professionals, patients, or caregivers); accidental exposure (particularly in children); and exposure of the patch to a heat source, possibly resulting in increased fentanyl absorption.

These reports also provide some evidence of inappropriate prescribing of fentanyl patches, including prescribing in unlicensed indications and in opioid-naïve patients.

A potent opioid analgesic

Fentanyl is a potent opioid analgesic—a 25 µg per hour fentanyl patch equates to daily doses of oral morphine of up to 90 mg. Fentanyl patches should be used only in patients who have previously tolerated opioids because of a risk of significant respiratory depression in opioid-naïve patients.

Initial dose should be based on a patient's opioid history. Information on starting doses and dose conversion can be found in the Summaries of Product Characteristics (SPCs), British National Formulary (BNF), British National Formulary for Children (BNFc), Palliative Care Formulary, and in local policies and guidance.

See http://emc.medicines.org.uk/ for SPCs; see also http://www.bnf.org/bnf/ or BNF p 232, 55th edn.

SPCs for fentanyl patches give detailed information on appropriate use to minimise the risk of life-threatening adverse reactions due to accidental exposure and overdose.

Advice for healthcare professionals:

- Healthcare professionals, particularly those who prescribe and dispense fentanyl patches, must fully inform patients and caregivers about directions for safe use:
  - follow the prescribed dose
  - follow the correct frequency of patch application
  - ensure that old patches are removed before applying a new one
  - patches must not be cut
  - avoid touching the adhesive side of patches and wash hands after application
  - follow instructions for safe storage and disposal of used or un-needed patches

  This information is given in the SPC for prescribers and in the package insert for patients
- Increased body temperature, exposure of patches to external heat sources, and concomitant use of CYP3A4 inhibitors may lead to potentially dangerous rises in serum fentanyl levels. Concomitant use of other CNS depressants might also potentiate adverse effects from fentanyl
- Healthcare professionals, particularly those who prescribe and dispense fentanyl patches, should ensure that patients and caregivers are aware of the signs and symptoms of fentanyl overdose—ie, trouble breathing or shallow breathing; tiredness; extreme sleepiness or sedation; inability to think, walk, or talk normally; and feeling faint, dizzy, or confused. Patients and caregivers should be advised to seek medical attention immediately if overdose is suspected
- Patients who experience serious adverse events should have the patches removed immediately and should be monitored for up to 24 hours after patch removal

Read SPCs and Patient Information Leaflets at http://emc.medicines.org.uk/

Examples of CYP3A4 inhibitors: ritonavir, nelfinavir, ketoconazole, itraconazole, clarithromycin, erythromycin, verapamil, diltiazem, and amiodarone

Examples of other CNS depressants: alcohol, other opioids, anxiolytics, hypnotics, general anaesthetics, antipsychotics, skeletal-muscle relaxants, and sedating antihistamines

See http://www.npsa.nhs.uk/patientsafety/alerts-and-directives/rapidrr/reducing-dosing-errors-with-opioid-medicines/

The UK National Patient Safety Agency has recently issued a Rapid Response Report on dosing errors with opioid medicines. The NPSA recommends that knowledge of previous opioid dose is essential for safe use of these products, and that when a dose increase is intended the calculated dose is safe for the patient.

Yellow Card Scheme update

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

For further information about black triangle drugs and vaccines, see *Drug Safety Update* July 2008, p 6. www.mhra.gov.uk/mhra/drugsafetyupdate

For further information on the online Yellow Card, see *Drug Safety Update* April 2008, p 6. www.mhra.gov.uk/mhra/drugsafetyupdate

For further guidelines on what to report on a Yellow Card please see https://yellowcard.mhra.gov.uk/hcp/hcp-guidelines/

For further detailed information on vaccines and vaccination procedures please refer to the Green Book: http://www.dh.gov.uk/en/Publichealth/Healthprotection/Immunisation/Greenbook/DH_4097254; see also Hot topic this issue p 5

Please report suspected adverse reactions to vaccines

This month's Hot topic (p 5) highlights key points on the introduction of human papillomavirus (HPV) immunisation for girls aged 12–13 years, starting from September 2008.

An important responsibility of the MHRA and the Commission on Human Medicines is to intensively monitor the safety of all new medicines or vaccines, which carry a black triangle (▼). Although new medicines and vaccines are extensively studied in clinical trials before marketing, it is important that we continue to monitor their safety during routine use.

Reporting

You can help us by reporting via the Yellow Card Scheme any suspected adverse reactions associated with vaccines. You can send Yellow Cards by post, but we strongly recommend reporting online at www.yellowcard.gov.uk. You can submit several reports at once online, and (if registered) keep a log of all your reports.

Online reports will also reach us more rapidly than those via post, helping us to take any necessary action promptly.

When reporting a suspected adverse reaction to a vaccine, please include the following:

- suspected adverse reaction(s): please report only the main diagnosis as the suspected side-effect; signs and symptoms can be included as additional information if necessary
- vaccine brand name
- vaccine batch number (if available)
- time to onset (if known)
- age and gender of the person who had the adverse reaction
- your contact details, should we need further information

Hot topic

- **Cervarix will be used in the UK routine HPV immunisation programme, starting in September 2008 for 12–13-year-old girls. There will also be a phased catch-up of girls up to age 18 years**
- **Please report suspected adverse reactions, adhering to the reporting guidelines outlined in this article; see also p 4**

Introduction of human papillomavirus immunisation in the UK

Infection with human papillomavirus is one of the most common sexually transmitted diseases. There are more than 100 different types of HPV, at least 13 of which can cause cancer (ie, high-risk types). Genital infection with a high-risk HPV virus is the main cause of cervical cancer: HPV types 16 and 18 are responsible for around 70% of cases. Some high-risk HPV infections are associated with cancer of the penis, vulva, vagina, anus, mouth, and oropharynx.

Most high-risk HPV infections are short-lived and cleared by the immune system within 2 years without any clinical consequences. Persistent infection is a necessary factor for development of high-grade precancerous lesions and cervical cancer. HPV causes nearly 3000 cases of cervical cancer every year in the UK.

HPV vaccines

Two HPV vaccines are licensed in the UK—Cervarix and Gardasil. Both protect against cervical cancer caused by HPV types 16 and 18 (Gardasil also protects against low-risk HPV types 6 and 11, which cause >90% of genital warts). The active ingredient in both vaccines is virus-like particles, which do not contain viral DNA and therefore cannot cause HPV infection.

Cervarix will be used in the UK routine HPV immunisation programme. The programme will start in September 2008 and involve annual immunisation of 12–13-year-old girls (school year 8). There will also be catch-up immunisation of girls up to age 18 years spread over 3 years. The timing of catch-up programmes may differ in Scotland, Wales, and Northern Ireland.

Cervarix is given as three doses over a 6-month period. Its safety and efficacy were extensively studied in clinical trials before licensing.[1-3] The commonest side-effects identified are injection-site reactions, fever, headache, fatigue, muscle pain, nausea, vomiting, and diarrhoea.

Reporting of suspected adverse reactions

The MHRA continuously monitors all vaccines and medicines used in the UK, including the safety of HPV vaccines. Please report suspected adverse reactions via the Yellow Card Scheme. You can send Yellow Cards by post, but we strongly encourage online reporting at www.yellowcard.gov.uk. When submitting a Yellow Card, please include vaccine brand name, batch number (if available), and all relevant clinical information to allow assessment of the case. In some cases we may need to contact you to obtain further information.

Faints and panic attacks during an immunisation session

Fainting (or vasovagal syncope) can occur during, following, or even before, vaccination. Some individuals may also experience panic attacks before vaccination. The clinical features of fainting and panic attacks are described in detail in chapter 8 of the Green Book.

Fainting can occasionally result in traumatic injury, and local procedures should be in place to observe and manage such events. It is important that any sudden loss of consciousness or generalised reaction is distinguished from a possible anaphylactic reaction.

Fainting and panic attacks can occur during any injection procedure. When an episode occurs during or very shortly after vaccination, it is highly unlikely to be a true side-effect of the vaccine itself and is most likely a psychogenic reponse to

Further information on the immunisation programme can be found on the NHS Immunisation website www.immunisation.nhs.uk/Vaccines/HPV

1 Harper DM, et al. *Lancet* 2004; **364**: 1757–65.
2 Harper DM, et al. *Lancet* 2006; **367**: 1247–55.
3 Paavonen J, et al. *Lancet* 2007; **369**: 2135–37.

See Yellow Card Scheme update p 4

Access the Green Book at http://www.dh.gov.uk/en/Publichealth/Healthprotection/Immunisation/Greenbook/dh_4097254

the injection process. Please use the Yellow Card Scheme to report only reactions that are suspected to be related to the vaccine and not those associated with the injection process.

For further information on the Yellow Card Scheme visit www.yellowcard.gov.uk

If having considered this advice, you wish to report an episode which may have been psychogenic, please include only the main diagnosis or event as the suspected reaction (eg, vasovagal syncope, faint, or panic attack). Please do not report as a suspected reaction any signs or symptoms associated with these events (eg, loss of consciousness, injury, limb jerking or tingling, difficulty in breathing, or hyperventilation). If necessary, they can be included as additional information on the Yellow Card if considered important.

Episodes of mass fainting or panic attacks (or both) can occur during a large immunisation session.[4] Please note the above reporting guidance, which will help us distinguish key safety issues associated with the vaccine from those that are injection-related events.

4 Clements CJ. *Drug Saf* 2003; **26:** 599–604.

Further information:

Further information from the MHRA
www.mhra.gov.uk/HPVvaccine

Product information from the European Medicines Agency
www.emea.europa.eu/htms/human/epar/a.htm

Summaries of Product Characteristics and Patient Information Leaflets
http://emc.medicines.org.uk/

NHS immunisation website
www.immunisation.nhs.uk/Vaccines/HPV

Health Protection Agency
www.hpa.org.uk

Reporting of anaphylaxis and other allergic reactions

Anaphylaxis is a very rare, side-effect of most vaccines. Chapter 8 of the Green Book gives detailed guidance on distinguishing between faints, panic attacks, and the clinical features of anaphylaxis. The table below shows the clinical features of fainting and anaphylaxis.

If you suspect a true case of anaphylaxis, please report it via the Yellow Card Scheme as a case of anaphylaxis (or if appropriate anaphylactoid reaction). Less-severe allergic reactions (ie, those that do not meet the full clinical features of anaphylaxis) should be reported as allergic reaction. Any relevant signs or symptoms should be reported only as additional information on the Yellow Card if considered important.

	Fainting	Anaphylaxis
Onset	Before, during, or within minutes of vaccine administration	Usually within 5 min, but can occur within hours of vaccine administration
Signs and symptoms		
Skin	Generalised pallor, cold clammy skin	Skin itchiness, pallor, or flushing of skin; red or pale urticaria (weals); or angioedema
Respiratory	Normal respiration—may be shallow, but not laboured	Cough, wheeze, stridor, or signs of respiratory distress (tachypnoea, cyanosis, rib recession)
Cardiovascular	Bradycardia, but with strong central pulse; hypotension—usually transient and corrects in supine position	Tachycardia, with weak or absent central pulse; sustained hypotension
Neurological	Sense of light-headedness; loss of consciousness—improves once supine or head-down position; transient limb-jerking and eye-rolling, which may be confused with seizure; incontinence	Sense of severe anxiety and distress; loss of consciousness—no improvement once supine or in head-down position

Source: The Green Book, chapter 8 (updated June 26, 2008), p 58.

Stop press

Viracept: update on carcinogen contamination (ethyl mesylate)

In June 2007, Viracept (**nelfinavir**, a HIV treatment) was recalled because of contamination with a genotoxic carcinogen called ethyl mesylate (EMS). New information from studies done by the marketing authorisation holder provide some reassurance that there is a threshold level below which EMS does not cause irreversible damage to DNA. Extrapolation from studies in mice suggests that this threshold level is approximately 2 mg/kg a day in humans: patients who took contaminated batches were exposed to about 0·05 mg/kg a day.

These new data suggest that patients who were exposed to EMS are not likely to be at an increased risk of developing cancer compared with patients with HIV who were not exposed to the contaminant. Similarly, pregnant women who were exposed to contaminated batches are not thought to be at increased risk of having a baby with birth defects.

For further information, see http://www.emea.europa.eu/humandocs/PDFs/EPAR/Viracept/38225608en.pdf

Natalizumab (Tysabri): progressive multifocal leukoencephalopathy

At the end of July 2008, two European cases of progressive multifocal leukoencephalopathy (PML) were reported in patients with multiple sclerosis who received **natalizumab** (Tysabri ▼).

In addition, two cases (one of which had a fatal outcome) occurred in patients given natalizumab combined with interferon beta in clinical trials before licensing. Combination therapy is contraindicated for natalizumab.

The two new cases occurred in patients given natalizumab alone for approximately 17 and 14 months, respectively. Both patients have had plasma exchange to remove the medicine from their circulation. There have been no cases of PML reported to date in the UK.

Advice for healthcare professionals:

- Natalizumab must be prescribed in strict compliance with the Summary of Product Characteristics and according to the Physician Information and Management Guidelines from the marketing authorisation holder
- A recent MRI should be available before initiation of treatment with natalizumab. During treatment, patients must be monitored regularly for any new or worsening neurological symptoms or signs that may suggest PML. If new neurological symptoms occur, treatment should be suspended until PML has been excluded
- Natalizumab must be permanently discontinued if a patient develops PML

Access the Summary of Product Characteristics at http://emc.medicines.org.uk/

For further information see *Drug Safety Update* June 2008, p 2; www.mhra.gov.uk/mhra/drugsafetyupdate

See also a letter for healthcare professionals sent Aug 15, 2008; http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/index.htm

As with all medicines, the safety of natalizumab remains under close review. Please continue to report to the MHRA and the Commission on Human medicines all suspected adverse reactions to natalizumab via the Yellow Card scheme at www.yellowcard.gov.uk.

Monthly round-up of letters to healthcare professionals

View monthly letters at http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/index.htm

Visit our website to view recent letters sent to healthcare professionals to inform of new safety information for particular medicines that might be relevant for your practice. In July and August 2008, letters were sent for: Humira ▼ (**adalimumab**, reports of hepatosplenic T-cell lymphoma); Avastin ▼ (**bevacizumab**, not for use in combination with sunitinib); and for Celance (**pergolide**, fibrotic reactions with chronic use).

Intrathecal drug pumps: missing propellant

In May 2008, the MHRA placed on its website a field safety notice about the risk from Medtronic SynchroMed II pumps (models 8637-20 and 8637-40) that had been manufactured without gas propellant. This defect potentially affects any pump manufactured before April 2007, but less than 1% of them are thought to be affected. Pumps produced after April 2007 are unaffected because of a process change at the manufacturing site.

Reservoirs in pumps without propellant cannot be fully aspirated. If implanted, they may deliver an unknown drug concentration or inconsistent or variable therapy, or may cease delivery completely without warning or alarm. The patient may experience a clinically significant drug underdose or overdose, a lack of therapeutic effect, a return of underlying symptoms, or withdrawal symptoms. No death or permanent injury has been reported in association with this issue. Risk is highest in those who are receiving baclofen treatment.

See http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/FieldSafetyNoticesformedicaldevices/CON020559

Identify potentially affected pumps at http://synchromed2propellant.medtronic.com

Advice for healthcare professionals:

- Ensure that potentially affected unimplanted units have been returned to Medtronic
- Identify patients who are implanted with potentially affected pumps
- In patients who have a potentially affected pump, follow the manufacturer's instructions to identify whether it is an affected pump at the patient's next refill session
- If a pump is identified as lacking propellant, immediate pump replacement should be considered

Caffeine for apnoea of prematurity: correction

An article about caffeine for apnoea of prematurity in the August 2008 issue of Drug Safety Update (p 9) should have read as follows in the 2nd paragraph:

"We are aware that different hospitals have been using unlicensed supplies of this medicine that have different product labelling—either caffeine 5 mg/mL or caffeine **citrate** 10 mg/mL."

Recall of reagent for paracetamol levels

See http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/FieldSafetyNoticesformedicaldevices/CON020827

In July 2008, the MHRA published a field safety notice from Beckman Coulter Inc about a recall of specific lots of Synchron **acetaminophen reagent** that had been manufactured with heparin that was contaminated with over-sulphated chondroitin sulphate (OSCS).

Acetaminophen is the assay used to measure paracetamol levels in plasma after an actual or suspected overdose. Results from affected batches show a falsely low reading at the low end of the measuring range by about 2 µg/mL. However, this false reading would not have any affect on the decision of whether to treat with acetylcysteine or methionine. Treatment lines should always be considered alongside other patient risk factors, and should be regarded as useful guides rather than strict cut-off points for treatment.

If you are aware of problems with acetaminophen or any other assays, please report them via the MHRA adverse incident centre online at www.mhra.gov.uk.

Other information from the MHRA

Patient Information Leaflet of the month: Prostasan (saw palmetto)

Access PIL of the Month at: http://www.mhra.gov.uk/Howweregulate/Medicines/Labelspatientinformationleafletsandpackaging/Patientinformationleaflet(PIL)ofthemonth/index.htm

Read more about the regulation of herbal medicines at: http://www.mhra.gov.uk/Howweregulate/Medicines/Herbalandhomoeopathicmedicines/Herbalmedicines/index.htm

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 enable 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 the herbal medicine **Prostasan**, which contains saw palmetto traditionally used for the relief of urinary discomfort in men with benign prostatic hypertrophy. This medicine has recently been registered under a scheme which began in 2005 to ensure herbal medicines meet specific standards of safety and quality, and are accompanied by agreed indications based on traditional use and by patient information that supports safe use of the product.

Azithromycin reclassification: pharmacy availability to treat chlamydia

See our News Centre: http://www.mhra.gov.uk/NewsCentre/index.htm

Clamelle (**azithromycin**) has been approved for pharmacy availability to treat **chlamydia**. The first oral antibiotic to be made available without prescription can be given to people older than 16 years who have tested positive for the infection and have no symptoms, and to their sexual partners. Clamelle is expected to be available in pharmacies later this year.

Further information is available on our website.

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

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Report a suspected adverse drug reaction at www.yellowcard.gov.uk