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

The **Medicines and Healthcare products Regulatory Agency** is the government agency which is responsible for ensuring that medicines and medicaldevices 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.

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This month, we focus on vaccines as we outline the safety experience with pandemic vaccines and the use of Cervarix in the human papillomavirus immunisation programme. Our proactive safety monitoring of these vaccines has proven to be a model on which to build a similar strategy for future major immunisation programmes in the UK. The safety profile of these vaccines has been very much as expected, and their benefits continue to outweigh any risks (see Hot topics).

Furthermore, we are requesting your particular help with the monitoring of all seasonal flu vaccines in children for the approaching flu season. In particular, prompt reporting of cases of febrile convulsion occurring within 72 hours of vaccination is vital—see article Y1 for more information. Report online at www.yellowcard.gov.uk [1]

Also this month, important news for professionals who fit the Implanon subdermal contraceptive implant. A new product, called Nexplanon, is replacing Implanon. Nexplanon is a radio-opaque version with a new insertion mechanism. All healthcare professionals who are trained in inserting Implanon will need to make sure they are trained in using Nexplanon before the changeover. This should include model-arm training with a placebo implant—see article A1 for further information.

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Drug safety advice

A1 Implanon contraceptive implant: changing to Nexplanon

In October 2010, Nexplanon replaces the Implanon contraceptive implant. Nexplanon is a radio-opaque version with a new insertion mechanism. All healthcare professionals who are trained in inserting Implanon will need to make sure they are trained in using Nexplanon before the changeover. This should include model-arm training with a placebo implant

Subdermal contraceptive implants containing etonogestrel

To date, the only available subdermal implant used for contraception in the UK has been Implanon, which contains 68 mg etonogestrel. In October this year, a new product—called Nexplanon—replaces Implanon. Nexplanon also contains 68 mg etonogestrel and is bioequivalent to Implanon. Similar to Implanon, Nexplanon can be used for up to 3 years, and is removed in the same way as Implanon.

What is changing?

Nexplanon differs from Implanon in two ways:

- it has a new preloaded applicator, designed to reduce the risk of insertion errors
- it is radio-opaque (it contains barium) and can therefore be located on an X-ray or CT scan, if necessary

Actions required: currently trained Implanon inserters

Practitioners who currently insert Implanon should become familiar with the new Nexplanon, and should complete both theoretical and practical training before attempting to use it. An online visual training programme includes animation of the insertion technique. Once completed, model-arm training with a placebo implant is strongly recommended. Further details about the training programme and how to obtain placebo devices can be found on the manufacturer's website: www.nexplanon.co.uk/training[3], or by contacting 0844 556 1444. Further details about training can also be found at the Faculty of Sexual and Reproductive Healthcare website www.frsh.org[4]

What will happen to current stock of Implanon?

Implanon will now be discontinued. However, you can continue to prescribe, dispense, or fit any remaining Implanon stock you may have.

Advice for healthcare professionals:

- It is essential that trained inserters of Implanon obtain practical and theoretical experience before changing to Nexplanon. This should include model-arm training with a placebo implant

See also letter for healthcare professionals sent September 2010[5].

Nexplanon is also our highlighted Patient Information Leaflet of the month (see article O1).

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Yellow Card Scheme update

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

See also letter sent to healthcare professionals sent Sept 13, 2010 [5] .

Y1 Yellow Card Scheme update: seasonal flu vaccines in children—prompt reporting of febrile seizures requested

We are requesting your particular help with the monitoring of all seasonal flu vaccines in children for the approaching flu season.

As a reminder, the Department of Health has advised against the use of two particular brands of seasonal influenza vaccine in children younger than age 5 years: Enzira and CSL Biotherapies generic influenza vaccine (both manufactured by CSL and marketed by Pfizer; for further information see the immunisation section of the Department of Health's website [6]).

Recent use of these vaccines in Australia was associated with an increased risk of febrile convulsions within 72 hours of vaccination (see the Australian Therapeutic Goods Administration website [7]). Approximately nine cases per 1000 doses were reported to the Therapeutic Goods Administration in Australia, and this risk appears to be product-specific to CSL's influenza vaccines. Children older than age 6 months and younger than 5 years who are in clinical risk-groups should still receive flu vaccination, but should use the alternative vaccines as recommended by the Department of Health (see letter from the Chief Medical Officer [8]).

Although there is no evidence that other seasonal flu vaccines carry this risk, it is important that we continue to closely monitor the safety of all flu vaccines. Please help us monitor the safety of flu vaccines by promptly reporting every case of febrile convulsion occurring within 72 hours of receiving the vaccine. It is vital that the brand name of the vaccine given, and batch number if available, are reported to us. However, if you do not have this information at hand, please still report to us and we will contact you for further information. Report online at www.yellowcard.gov.uk [1]. Alternatively, you can report by post (paper Yellow Cards are available at the back of the British National Formulary, or call 0800 731 6789).

See also our Hot topic this month for a summary of the safety profile of pandemic antivirals and vaccines.

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Hot topic

H1 Pandemic vaccines and antivirals: safety review

Overall, the safety profile of pandemic vaccines and antivirals has been very much as expected. Here, we outline the safety experience of these medicines in the UK from our proactive safety monitoring strategy

On June 11, 2009, WHO declared an official influenza pandemic (phase 6), reflecting global spread of a new strain of human flu H1N1 virus. A UK-wide strategy of offering a flu antiviral (oseltamivir or zanamivir) to everyone with flu-like illness was implemented. In October 2010, a mass immunisation campaign with the novel pandemic H1N1 influenza vaccines Pandemrix and Celvapan commenced across the UK. Vaccine was offered to all front-line health and social -care workers, those at increased risk of flu complications, and healthy children. Although there was already substantial clinical experience with the antivirals, there was no post-licensing experience with the vaccines.

Real-time safety monitoring

We developed a proactive, real-time safety monitoring strategy to meet the challenges of the pandemic. This involved:

- development of a dedicated online portal for reporting suspected adverse reactions to pandemic vaccines and antivirals
- statistical analysis of the number of observed adverse events versus those that would be expected to occur in the absence of receiving a pandemic vaccine or antiviral, to detect new safety signals
- weekly publication of the emerging safety profile

See also Drug Safety Update February 2010 [10] for further information on the pandemic safety profile and www.mhra.gov.uk/swineflu [11]

Pandemic vaccine safety profiles

To date, at least 6 million doses of Pandemrix and at least 30 000 doses of Celvapan have been given in the UK. As at June 18, 2010, 3400 and 43 suspected adverse reactions were reported to the MHRA in association with Pandemrix and Celvapan, respectively. It is estimated that at least 30 million and 566 000 people have been vaccinated with Pandemrix and Celvapan, respectively, across the EU during the pandemic.

In the UK, use of Celvapan was limited to those for whom Pandemrix was not suitable. On the basis of the few reports received in association with Celvapan, no new safety concerns have emerged in the UK; similarly, no significant safety issues have arisen in the EU (see the influenza update section of the European Medicines Agency website [9]).

Guillain-Barré syndrome

During the pandemic, the MHRA received 15 suspected reports of Guillain Barré Syndrome (GBS) in temporal association with Pandemrix vaccine; not all cases had the diagnosis confirmed. It was evident from our analyses early in the vaccination programme, including similar analyses across the EU, that there was no clear indication of a large increased risk of GBS similar to that seen with swine flu vaccines in the US in 1976. To date, there remains no confirmed evidence to indicate that Pandemrix or Celvapan is associated with an increased risk of GBS. However, given the uncertainties in the available information and as with seasonal flu vaccines, a slightly elevated risk of GBS following H1N1 vaccines cannot be completely ruled out. The benefits of vaccination would still outweigh any small vaccine-attributable risk of GBS. Epidemiological studies are ongoing to further assess this possible association.

Febrile seizures in children

Clinical trial data for Pandemrix showed that in children aged from 3 months to 6 years, the second dose (half the adult dose) was associated with greater reactogenicity compared with the first, particularly shown as higher fever rates—likely to increase the risk of febrile convulsion. The MHRA received 12 reports of febrile seizures in children, all in the age-group within which febrile convulsions usually occur. Product information for Pandemrix was amended in December 2009 to warn of the risk of fever, and the possibility of febrile seizures, and to allow for one or two doses to be given to children. Other than the risk of higher rates of fever after a second dose, there is no indication of any new or specific safety concerns in children.

See this month's Yellow Card Scheme update for information on the risk of febrile seizures with seasonal vaccination.

Summary

Overall, the safety profile of both vaccines was very much as expected, and broadly similar to the established profile for seasonal influenza vaccines. Most suspected adverse reactions were injection site reactions or signs and symptoms of mild 'flu-like illness'.

Antivirals safety overview

During the pandemic, more than 1 million courses of oseltamivir and more than 14 000 courses of zanamivir were supplied to patients in the UK. During this time, the MHRA received 1100 suspected adverse reactions in association with oseltamivir and 38 in association with zanamivir. The safety profile of oseltamivir and zanamivir in the UK has been broadly in line with the expected profile: no new safety issues have been confirmed for either antiviral during the pandemic.

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Hot topic

H2 Human papillomavirus immunisation programme: second year safety review

No new risks have been identified for Cervarix despite significant exposure in the UK, and the balance of risks and benefits remains positive. This article summarises the safety experience of the past 2 years

The human papillomavirus (HPV) immunisation programme has now completed its second successful year and is ready to enter its third. With at least 4·5 million doses of Cervarix administered up to the end of July 2010 to girls aged 12–18 years across the UK, the vaccine has been shown to have an excellent safety profile. Most Yellow Card reports have related either to the signs and symptoms of recognised, minor side effects listed in the product information, or to the injection process and not the vaccine itself (ie, psychogenic in nature).

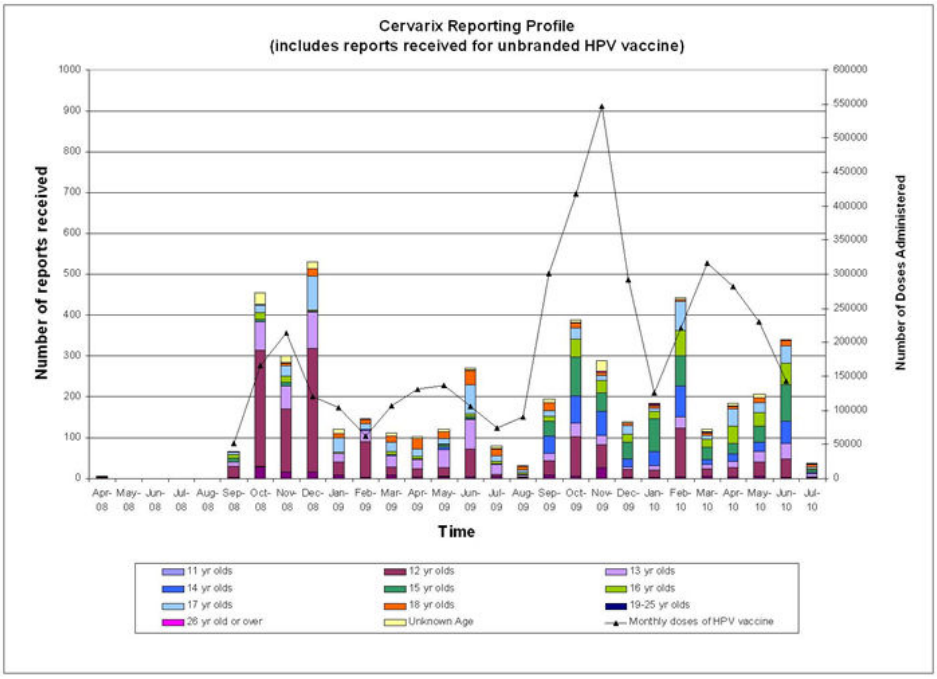
Safety monitoring strategy

Our proactive and transparent approach to safety monitoring for the HPV vaccine during its first 2 years of use has enabled real-time, scientifically robust analysis of vaccine safety. This strategy involved daily analysis of all suspected adverse reactions, and weekly publication of safety reports (see www.yellowcard.gov.uk [1] and www.mhra.gov.uk/hpvvaccine [12]). The approach has provided reassurance on events likely to be coincidental to the vaccine, and helped to minimise unfounded concerns among parents and teenagers. As with all vaccines and medicines, the MHRA will continue to keep the safety of Cervarix vaccine under close review.

Cervarix: current safety profile

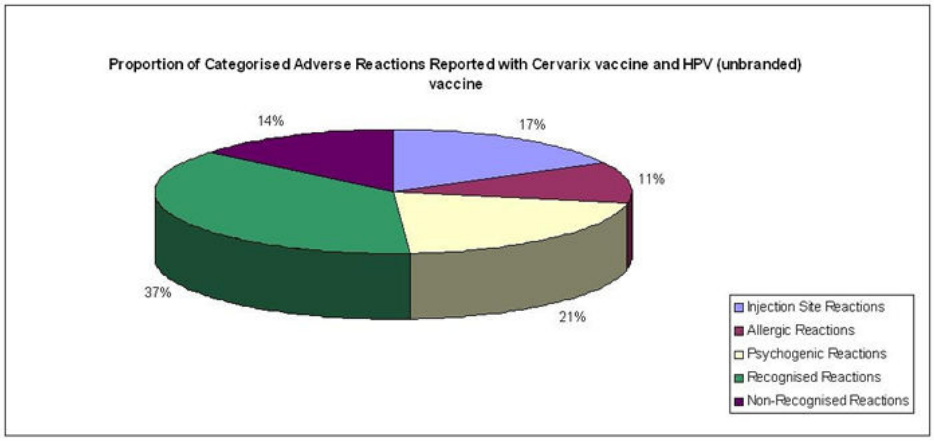
Up to the end of July 2010, we received 4703 Yellow Cards, including 10,410 adverse-reaction terms, in association with Cervarix (including reports in which the brand of HPV vaccine was not stated by the reporter). The reporting profile is very much in line with that of the first year of the programme (see Drug Safety Update October 2009 [13]), and the total number of reports received over the past 2 years of the programme is consistent with that expected.

Number of reports received per month September 2008–July 2010:



As expected, most reports to date have been in girls aged 12–13 years and have been submitted by nurses (mostly school nurses).

The type of adverse reactions reported to the Yellow Card Scheme:



Most reports continue to be related to minor reactions already recognised and listed in the product information, or to 'psychogenic' events such as faints, which are not due to the vaccine per se but to the injection process. 'Psychogenic' events are relatively common in adolescent immunisation programmes. More information on the proportion of categorised adverse reactions reported can be found at www.mhra.gov.uk/hpvvaccine [12].

Other adverse events assessed

All reported adverse events which are not currently recognised as possible side effects have been assessed. Most related either to isolated cases or small clusters of cases that are naturally occurring medical conditions among teenage girls. The available information does not indicate any consistent clinical pattern that may suggest an association with Cervarix. Given that at least 4·5 million doses have been administered to date, it is inevitable that many clinical events will occur in temporal association with vaccination, regardless of a causal association. Such events may be due to underlying/undiagnosed concurrent illness unrelated to vaccination.

Chronic Fatigue Syndrome and associated conditions

- CFS is a condition that occurs naturally among the population of girls vaccinated. Among the number of girls immunised so far in the UK, at least 100 cases of CFS would have been expected to have occurred by chance alone. Accounting for various levels of possible under-reporting to the Yellow Card Scheme, the reports so far in the UK do not indicate that Cervarix is a cause of CFS.

Guillain-Barré syndrome

- Five cases of Guillain-Barré syndrome (GBS) have been reported via the Yellow Card Scheme so far, with no consistent pattern of clinical presentation. Given the expected background incidence of GBS in the vaccinated population, our analyses have suggested that the reported cases are consistent with these being coincidental with vaccination.

Encephalitis

- The five cases of encephalitis reported so far among the number of girls immunised, does not exceed the overall number of cases we would normally expect in the absence of vaccination. As with CFS and GBS, encephalitis naturally occurs in the population and is most often caused by a preceding viral infection. There is no suggestion at present that the vaccine can cause encephalitis. As with other reported events, this will remain under review.

Summary

The Government's independent expert advisory Commission on Human Medicines (CHM) has scrutinised our 2-year safety analysis and agreed that the number and nature of suspected adverse reactions received since the vaccination programme started is fully in line with what we expected to receive at this time. CHM advised that 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. We will continue to monitor closely the safety of Cervarix during routine use in the UK.

Have you reported a Yellow Card for the HPV vaccine?

Thank you once again to those who have contributed to the success of this monitoring by sending us Yellow Cards for Cervarix. We encourage healthcare professionals involved in immunisation to 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. You can report online at www.yellowcard.gov.uk [1] or by post (paper Yellow Cards are available at the back of the British National Formulary or call us on 0800 731 6789). Remember that parents and vaccinees can also report suspected side effects on a Yellow Card.

Further information is available in a safety report available online at www.mhra.gov.uk/hpvvaccine [12]

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Hot topic

H3 Codeine-containing liquid over-the-counter medicines: should not be used for cough under 18 years

We have completed an evaluation of the benefits and risks of OTC oral liquids containing codeine for the treatment of cough in children, based on all available data. These products are currently available for supply by a pharmacist.

Risks and benefits of codeine as a cough suppressant

The Commission on Human Medicines and its Paediatric Medicines Expert Advisory Group have advised that codeine-containing OTC liquid medicines should not be used for cough suppression in children and young people younger than age 18 years.

Timing

Manufacturers are currently updating the packaging and leaflets for OTC liquid cough medicines that contain codeine to include the updated advice. The new information will begin to appear in pharmacies from April 2011, and in the meantime existing packaged medicines will continue to be sold and pharmacists have been asked to consider the new advice when recommending cough medicines for children.

Coughs and colds are self-limiting conditions

Coughs and colds occur frequently in children, but they are self-limiting and rarely harmful if left untreated. Coughs have a physiological function of clearing mucus secretions from the airways. Many medicines given to children have not been properly studied in this age-group. Specific paediatric studies are needed because of differences between adults and children in drug handling or drug effects, which may lead to different dose requirements.

In February 2009, we announced a package of measures to ensure safer use of other over-the-counter (OTC) cough and cold medicines for children younger than age 12 years. The MHRA is working to improve the availability of high-quality, ethically researched and properly authorised medicines for children.

Further information about the safer use of other over-the-counter (OTC) cough and cold medicines for children younger than age 12 years see our website [16]; see also Drug Safety Update April 2009 [17].

Information on medicines for children is also available on our website [18].

Reminder: codeine and very rare risk of side effects in breastfed babies

Healthcare professionals are reminded that breastfed babies might very rarely develop side effects due to the presence of morphine in breast milk. Further information is available from the November 2007 issue of Drug Safety Update [14].

Further information

Further information on the review of the benefits and risks of OTC oral liquids containing codeine for the treatment of cough in children is available in a report available on our website [15].

Article citation: Drug Safety Update Oct 2010, vol 4 issue 3: H3.

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Stop press

S1 Rosiglitazone: recommended withdrawal from clinical use

The European Committee on Medicinal Products for Human Use has recommended the suspension of the marketing authorisations of rosiglitazone (Avandia, Avandamet) across the European Union.

The UK Commission on Human Medicines has reviewed the available data and has concluded that there is an increased cardiovascular risk for rosiglitazone. It has not been possible to identify additional measures that would reduce the cardiovascular risk or to identify a patient population in whom the benefits continue to outweigh the risks. The Commission has therefore concluded that the benefits of rosiglitazone no longer outweigh its risks.

Advice for healthcare professionals and patients:

- Prescribers should put in place a system to ensure that all patients are reviewed and changed to another suitable treatment in line with NICE recommendations
- While this change could happen at the next routine appointment, prescribers may wish to see patients sooner rather than later in order to reduce patient anxiety
- Patients who are concerned should not stop their treatment but should contact the healthcare professional supervising their diabetic treatment

Further information is available on our website [19]; see also letter for healthcare professionals sent Oct 1, 2010 [5].

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S2 Octagam intravenous immunoglobulin 5% and 10%: recall due to thromboembolic events

We have issued a drug alert [20] to recall all remaining stock of Octagam 5% and 10% intravenous immunoglobulin solutions for infusion because of an unexpected increase in reported cases of thromboembolic events, including stroke, myocardial infarction, and pulmonary embolism.

Advice for healthcare professionals:

- Do not use any unused vials of Octagam 5% and Octagam 10%
- Quarantine and return all unused stock with immediate effect and seek alternative supplies of intravenous immunoglobulin
- Be extra vigilant for signs of a thromboembolic event in patients who have very recently received Octagam
- Report any suspected thromboembolic events that have occurred in association with Octagam on a Yellow Card at www.yellowcard.gov.uk [1]

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S3 Mercaptamine and mercaptopurine: confusion between drug names

We have been made aware of a medication error in which a 9-month-old who should have been prescribed mercaptamine by their GP was erroneously prescribed mercaptopurine. After about 1 month of incorrect therapy, the child was admitted to hospital with pancytopenia; the child has now made a full recovery.

We would like to remind prescribers to remain vigilant with regards to the similarity of these two drug names.

Mercaptamine is indicated for the treatment of proven nephropathic cystinosis. Mercaptopurine is indicated for the treatment of acute leukaemia.

Suspected adverse drug reactions, including those arising from medication errors, should be reported on a Yellow Card (see www.yellowcard.gov.uk [1]).

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Other information from the MHRA

O1 Patient Information Leaflet of the month: Nexplanon

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 supporting safer use of 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 example in the series is the leaflet for **Nexplanon contraceptive implant** to coincide with the introduction of the new product (see this month's drug safety advice section). The leaflet has been designed to highlight the key information and uses good navigation tools. In testing the leaflet was well received by patients. The examples of leaflets in this feature can be found on our website [21].

Article citation: Drug Safety Update October 2010, vol 4 issue 3: 01.

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1. http://www.yellowcard.gov.uk/
2. http://www.evidence.nhs.uk/Accreditation
3. http://www.nexplanon.co.uk/training
4. http://www.frsh.org/
5. http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/
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