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Second Pandemic pharmacovigilance weekly update

This update has been prepared by the European Medicines Agency to provide a summary of the adverse drug reactions reported after use of centrally authorised pandemic vaccines and antivirals. It also provides information on the evolution of the H1N1 pandemic, an estimate of how many doses have been distributed or administered in Europe, and other available information on the benefits and risks of the vaccines and antivirals. Centrally authorised pandemic medicines concerned by this update are the vaccines Celvapan, Focetria and Pandemrix and the antiviral Tamiflu.

This update includes reports of *suspected* reactions that were observed after the vaccines were administered. This does not mean that these reactions have been caused by the vaccine. They could be a symptom of another illness or they could be associated with another product taken by the patient. Healthcare professionals are actively encouraged to report events following vaccination. However, due to differences in the numbers of persons having received each vaccine, the number of reports shown for the three different vaccines cannot be used for a comparison between them regarding safety or benefit-risk.

Reports are collected on a continuous basis in EudraVigilance. EudraVigilance is a database and management system managed at the European Medicines Agency for collecting and evaluating reports of suspected adverse drug reactions to medicinal products. It allows the transfer of reports from National Regulatory Agencies and Marketing Authorisation Holders to the European Medicines Agency, and the early detection and monitoring of possible safety signals in relation to reported adverse reactions. This update includes reports received in EudraVigilance after the marketing authorisation of the centrally authorised pandemic vaccines and antivirals up to 1 December 2009. The graphs represent aggregated data related to the European Economic Area (EEA) only, and provide an overview of the reporting situation in the EEA. The updated safety information considers also worldwide cases contained in EudraVigilance.

Following comments received from readers after the publication of the first update, changes have been made in the presentation of the data. In this second update, the graphs present the cumulative number of patients having experienced one or more reactions in each organ system rather than the number of reactions. Therefore, these graphs cannot be compared with the graphs of the first update. A list of the most frequently reported suspected adverse reactions is also presented for the organ systems with the largest number of reports. A single patient may experience several reactions that will be included in a single report. Therefore the number of reactions may not be equal to the number of patients.

The weekly update may also include information on vaccine safety made available by Member States.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Key message:

The benefit-risk balance of the pandemic vaccines and antivirals used for the current H1N1 influenza pandemic continues to be positive. To date, no unexpected serious safety issues have been identified. The most frequent adverse reactions that have been reported are non-serious and as expected.

In a press release issued on 4 December 2009, the European Medicines Agency warned that young children may experience fever particularly after their second dose of the pandemic influenza vaccine Pandemrix. As with all vaccines, prescribers and parents should monitor the temperature of the vaccinated child and, if necessary, take measures to lower the fever (e.g. giving an antipyretic such as paracetamol). However, based on currently available data, the European Medicines Agency noted that the second dose increases the immune response against pandemic influenza.

Up to 1 December 2009, a total of five cases of possible Guillain-Barré syndrome have been reported following administration of pandemic vaccines. Guillain-Barré syndrome is a naturally occurring medical condition, most often due to a gastrointestinal or respiratory infection. Two to four cases of Guillain-Barré syndrome occur every year per every 100,000 people in the population in the 18-65 years of age category. Therefore, as more than 15 million people have now been vaccinated across the European Union (EU), these few cases do not exceed the number of expected cases (background frequency). There is no indication that the vaccination contributed to the occurrence of Guillain-Barré syndrome.

For further information on the established adverse reactions included in the authorised product information for centrally authorised pandemic vaccines (Celvapan, Focetria, Pandemrix) and antivirals (Tamiflu), visit the EMEA Pandemic influenza (H1N1) website.

For information regarding products authorised at a national level, please contact the relevant National Competent Authority (see the EMEA website for links).

Pandemic information:

According to the European Centre for Disease prevention and Control (ECDC) (for latest report click here), a total of 1024 fatal cases in the EU and EFTA countries and 8610 in the rest of the world have been reported up to date (see also the ECDC website (http://www.ecdc.europa.eu/en/Pages/home.aspx).

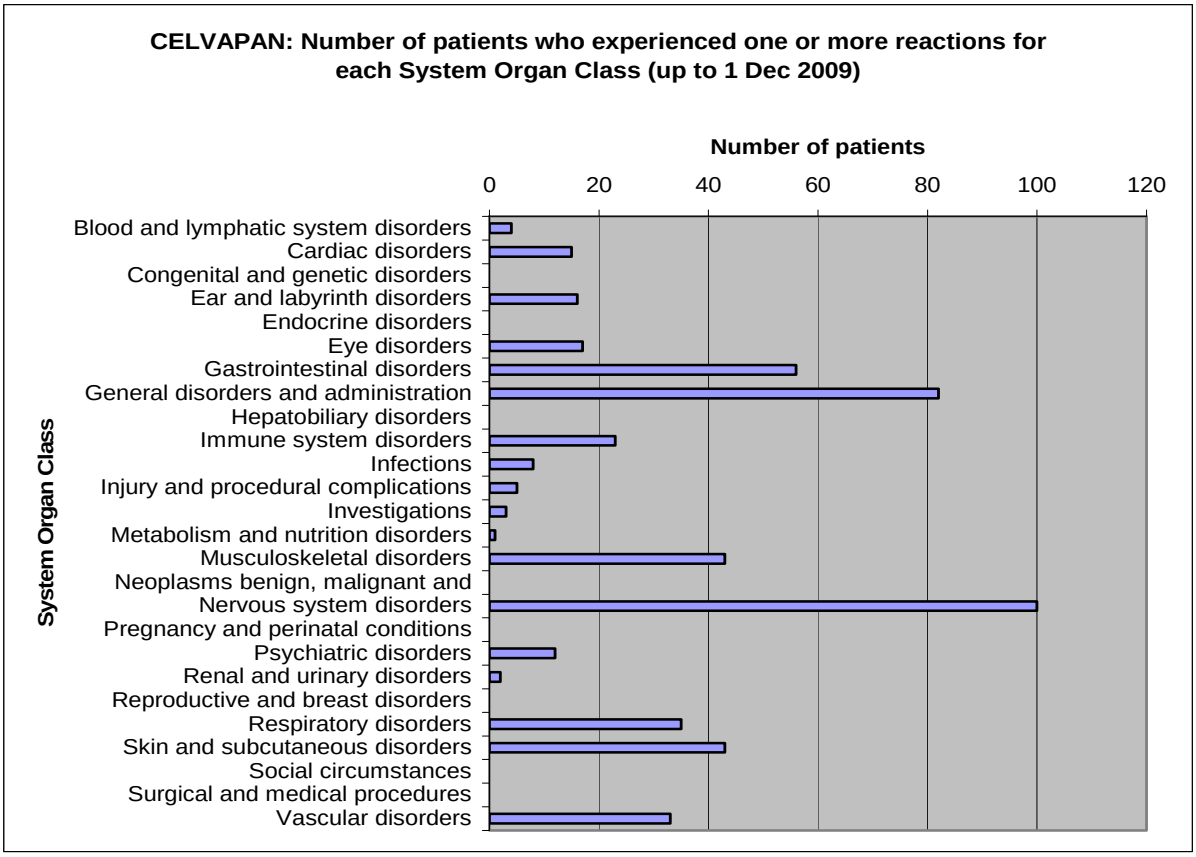
In its report of 2 December 2009, (http://www.who.int/csr/disease/swineflu/notes/briefing_20091202/en/index.html) the World Health Organization (WHO) gives information about patients infected with oseltamivir-resistant H1N1 viruses in two hospitals. These patients had severely compromised or suppressed immune systems and have been thoroughly investigated. Although transmission of resistant virus from one patient to another is suspected, other results are reassuring. Advice on treatment options for these highly vulnerable patients has been provided.

Overview of centrally authorised vaccines

As of 1 December 2009, a total of 5,301 reports have been received by EudraVigilance since the authorisation of the three centrally-authorised vaccines. This represents an increase of 1,469 reports compared with the previous update. This increase reflects the increase in the number of vaccinated people. Data available on 4 December 2009 indicate that at least 50 million doses of vaccine have been distributed and at least 15 million patients have been vaccinated in the EEA. From limited information received from 5 countries by 4 December 2009, at least 123,000 pregnant women have been vaccinated.
The graphs presented below include all reports received from the EEA. Updated safety information may include data received from outside the EEA.

Celvapan

As of 1 December 2009, a total of 191 reports have been received in EudraVigilance (increase of 31 reports since the previous update). According to company information, a total of 3,399,200 doses have been distributed to EU Member States through 16 November 2009.[1] On the basis of the available data, the number of doses administered could not be estimated.



Updated safety information:

- The most frequent suspected adverse reactions experienced by patients in each System Organ Class (SOC) since the authorisation of the vaccine are:
  - SOC Nervous system disorders: headache, dizziness, paraesthesia, hypoaesthesia;
  - SOC General disorders and administration site conditions: pyrexia, malaise, fatigue, chills, pain;
  - SOC Gastrointestinal disorders: nausea, vomiting;
  - SOC Skin and subcutaneous conditions: hyperhydrosis, pruritus, rash, urticaria;
  - SOC Musculoskeletal disorders: arthralgia, myalgia;
  - SOC Vascular disorders: pallor, flushing, hypotension;
  - SOC Respiratory disorders: dyspnoea, cough, oropharyngeal pain;
  - SOC Immune disorders: hypersensitivity, anaphylactic reaction.

- Since the authorisation, one fatal case was reported from the EEA. It concerns a male patient aged 57 years with underlying diabetes and cardiac disease, who died from an unknown cause of death 10 days after vaccination. There is no indication that the vaccine contributed to the death.

- Since authorisation, the most frequently reported suspected adverse reactions in children are hypersensitivity, vomiting and headache. Since the last update, four reports of syncope and three reports of blurred vision have been reported in children.

[1] As stated by the marketing authorisation holder in the simplified Periodic Safety Update Report (S-PSUR) received 30 November 2009.

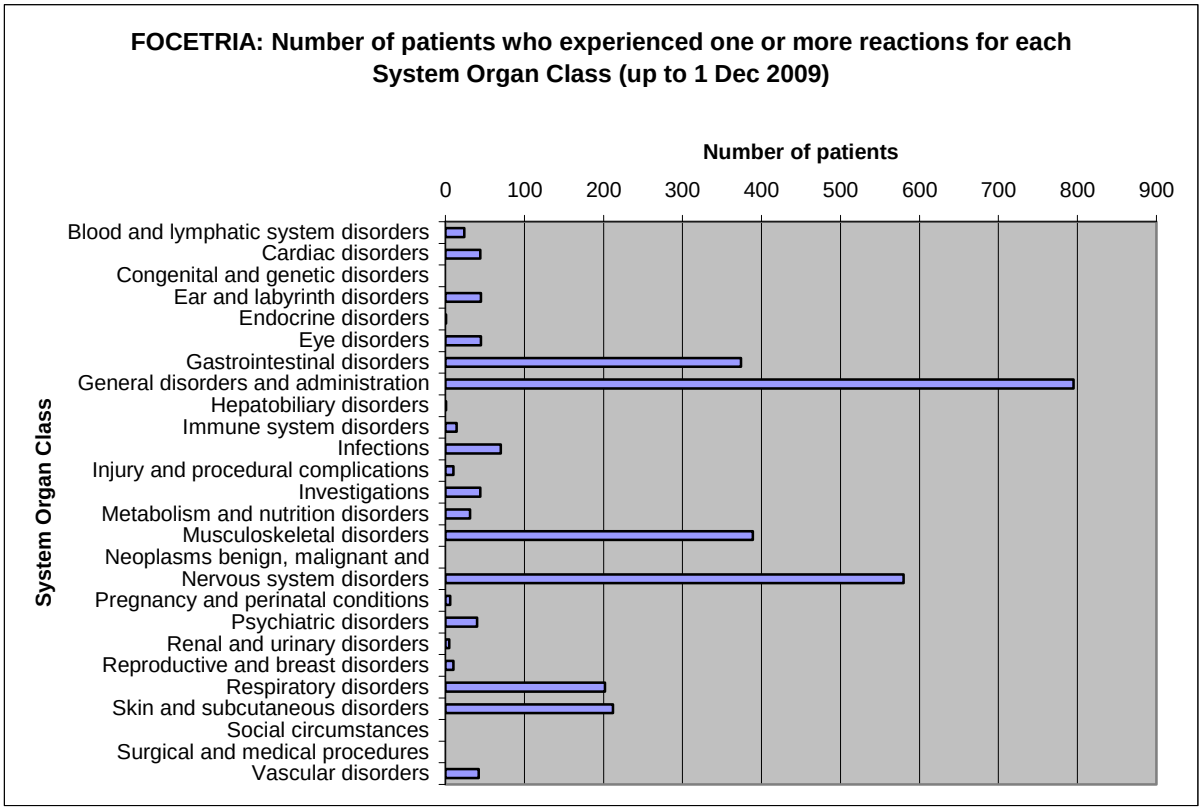
- Since authorisation, no cases of a pregnancy complication have been reported.

- The marketing authorisation holder conducted a review of all spontaneous reports of paraesthesia, anaphylaxis/angioedema and hypersensitivity. These possible reactions are being considered for addition to the Celvapan product information.

In summary, no unexpected safety issues have been detected since authorisation.

Focetria

As of 1 December 2009, a total 1,570 reports have been received in EudraVigilance (increase of 199 reports since the previous update). According to company information dated 16 November 2009, 10 million doses have been distributed through 2 November 2009.[2] It is estimated that at least 4.5 million doses have been administered.



Based on a recalculation of the number of reactions/cases presented in last week's update, the numbers of patients presented above supersede the data presented last week, and should be used for reference purposes.

Updated safety information:

- The most frequent suspected adverse reactions experienced by patients in each SOC since the authorisation of the vaccine are:

    - SOC General disorders and administration site conditions: pyrexia, malaise, injection site reaction, fatigue, chills, influenza-like illness;
    - SOC Nervous system disorders: headache, dizziness, paraesthesia, dysgeusia, presyncope;

[2] As stated by the marketing authorisation holder in the S-PSUR received 16 November 2009.

- SOC Musculoskeletal disorders: myalgia, arthralgia, pain in extremity, musculoskeletal stiffness;
- SOC Gastrointestinal disorders: nausea, diarrhoea, vomiting, abdominal pain;
- SOC Skin and subcutaneous conditions: hyperhydrosis, erythema, pruritus, rash, urticaria;
- SOC Respiratory disorders: dyspnoea, cough, oropharyngeal pain;
- SOC Infections: nasopharyngitis, rhinitis.

- Since authorisation, a total of 12 fatal cases were reported in the EEA. There is no indication that the vaccine contributed to these deaths.

- Since authorisation, the safety profile in children has been comparable to that in adults, with the most frequently reported suspected adverse reactions being pyrexia, headache, injection site reactions, nausea, vomiting, abdominal pain and influenza-like illness.

- Since authorisation of the vaccine, eight reports of pregnancy-related adverse events have been received (six EEA, two non-EEA). They included a report of abortion and a report of intrauterine death. At the moment there is no evidence that these events are related to the vaccine.

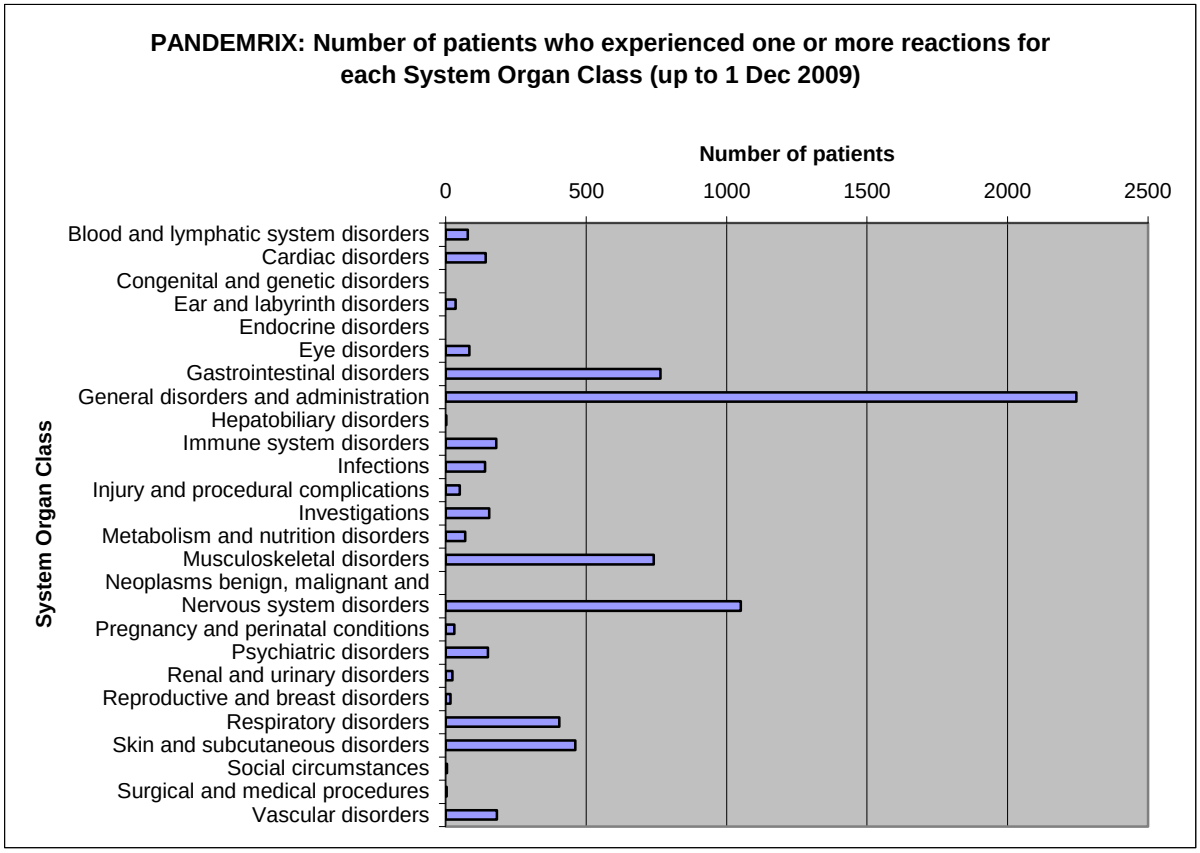
- Since the last update, one case of Guillain-Barré syndrome in a patient receiving treatment for cancer and one case of acute disseminated encephalomyelitis were reported. There is no indication that the vaccine contributed to these events. One case of anaphylactic shock was reported in a child with a history of asthma and hypersensitivity to chicken-egg proteins. The product information states that patients with serious allergies to any ingredient of Focetria should not receive this vaccine.

In summary, no unexpected safety issues have been detected since authorisation.

Pandemrix

As of 1 December 2009, a total of 3,540 reports have been received in EudraVigilance (increase of 1,239 reports since the previous update). According to the information received from the marketing authorisation holder dated 19 November 2009, the total number of doses distributed was 39.3 million.[3] The total number of people vaccinated is estimated to be larger than 11 million.

[3] As stated by the marketing authorisation holder in a report received on 19 November 2009.



Updated safety information:

- The most frequent suspected adverse reactions experienced by patients in each SOC since the authorisation of the vaccine are:

  - SOC General disorders and administration site conditions: pyrexia, injection site reaction, fatigue, malaise, influenza-like illness, chills, oedema peripheral, pain, asthenia;
  - SOC Nervous system disorders: headache, dizziness, paraesthesia, hypoaesthesia, convulsions, syncope, tremor, somnolence, lethargy, loss of consciousness, migraine, crying, facial palsy;
  - SOC Musculoskeletal disorders: myalgia, arthralgia, pain in extremity, musculoskeletal stiffness, muscular weakness, back pain, neck pain;
  - SOC Gastrointestinal disorders: nausea, diarrhoea, vomiting, abdominal pain;
  - SOC Skin and subcutaneous conditions: rash, erythema, pruritus, hyperhydrosis, urticaria;
  - SOC Respiratory disorders: dyspnoea, cough, oropharyngeal pain, tachypnoea, pharyngeal oedema, epistaxis;
  - SOC Vascular disorders: pallor, flushing, pallor, circulatory collapse;
  - SOC Immune disorders: anaphylactic reaction, hypersensitivity;
  - SOC Cardiac disorders: palpitations, tachycardia.

- Since authorisation, 24 reports of anaphylactic shock have been received. According to previous experience with other vaccines, anaphylaxis following vaccination is estimated to occur at a rate of 1 to 10 cases per 1 million doses distributed. Anaphylaxis is a rare expected adverse reaction with all injectable vaccines.

- Since authorisation, a total of 60 fatal cases were reported in the EEA. There is no indication that the vaccine contributed to these deaths. Pre-existing disease was a likely cause of death in the vast majority of cases.

- Since authorisation, the safety profile in children has been comparable to that in adults, with the most frequently reported suspected adverse reactions being pyrexia, headache, injection site reactions, cough, decreased appetite, nausea, vomiting, abdominal pain, rash, myalgia and

somnolence. Since the last update, a case of a non-serious photosensitivity reaction has been reported in a 2-year old girl with a latency of five hours following vaccination.

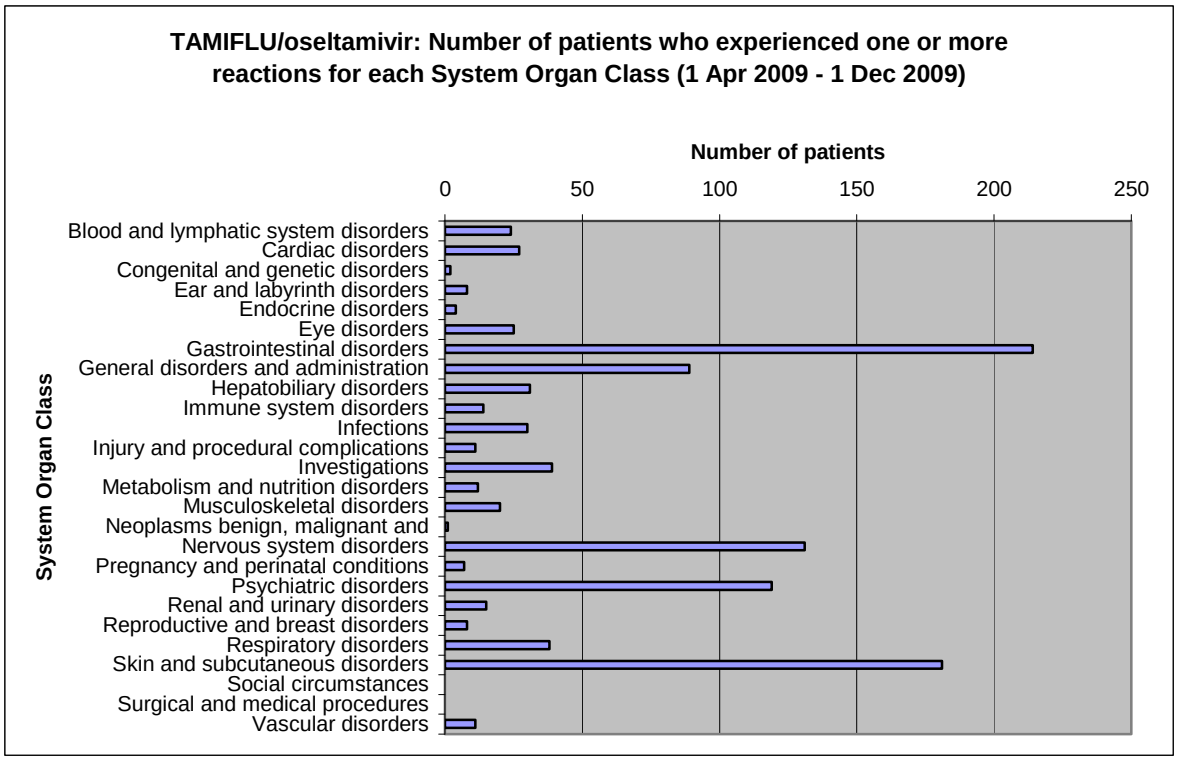
- Since authorisation, a cumulative total of 27 cases of pregnancy-related events such as miscarriages, intrauterine deaths, stillbirths, foetal hypokinesia and premature birth were received. Considering the number of pregnant woman vaccinated so far, there currently is no evidence of a causal link between the vaccine and reported events.

- The European Medicines Agency has been informed of two cases of transplant rejection observed in Sweden following administration of Pandemrix. There are grounds to consider that these episodes are not related to the vaccines, as non-compliance with therapy, and a previous episode of rejection were noted in these cases. Investigations are ongoing to estimate the proportion of transplanted patients who have been vaccinated with Pandemrix and to identify whether possible transplant complications may occur after vaccination.

Antiviral medicines:

Tamiflu

From 1 April to 1 December 2009, a total number of 734 reports (worldwide) have been received in EudraVigilance (increase of 29 reports since the previous update).
According to information received from the marketing authorisation holder dated 5 November 2009, the patient exposure during the period October 2008 to September 2009 was 10.4 million patients.[4]



Updated safety information:

- The adverse reaction reports received from the EEA are consistent with the safety profile described in the product information. The most frequent reported suspected adverse reactions experienced by patients in each SOC:

  - SOC Gastrointestinal disorders: vomiting, nausea, abdominal pain;
  - SOC Skin and subcutaneous conditions: rash, urticaria, pruritus, erythema multiforme;

[4] As stated by the marketing authorisation holder in the PSUR dated 5 November 2009.

- SOC Nervous system disorders: headache, convulsion, dizziness;
- SOC Psychiatric disorders: hallucinations, confusional state, anxiety;
- SOC General disorders and administration site conditions: malaise, death, chest pain, pyrexia.

- Since 1 April 2009, 145 case reports worldwide have been received by the EudraVigilance system with a fatal outcome following oseltamivir use, including 21 fatal cases from the EEA. For these fatal cases, a causal association with Tamiflu treatment has not been established. It should be noted that healthcare professionals are actively encouraged to report events following administration of medicinal products and coincidental events (e.g. due to underlying medical conditions) that would have occurred anyway, in the absence of therapy.