16 December 2009
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Patient Health Protection

Third 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. The 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 medicines were administered. This does not mean that these reactions have been caused by the medicine. 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.

It should be noted that, 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 balance.

Reports are collected on a continuous basis in EudraVigilance. EudraVigilance is a database and management system managed by the European Medicines Agency for the collection and evaluation of 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 up to 6 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 also considers worldwide cases from EudraVigilance. 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 the safety of vaccines made available by Member States.

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Key message

At least 26 million persons and 213,000 pregnant women have been vaccinated to-date in Europe with one of the three centrally-authorised vaccines. No unexpected serious safety issues have been identified. The most frequent adverse reactions that have been reported are non serious and as expected.

The benefit-risk balance of the pandemic vaccines and antivirals used for the current H1N1 influenza pandemic continues to be positive.

A cumulative review of all fatal cases received for any of the three vaccines since authorisation has shown that the majority of them were explained by pre-existing medical conditions, mainly cardiovascular disorders such as coronary heart disease. Follow-up information is expected for the small number of cases where information is still lacking.

Two cases of transplant rejection observed in Sweden following administration of Pandemrix were discussed in the second weekly Update. Further investigation has shown that, as of 13 December 2009, no other cases have been reported within the EU despite targeted immunisation of transplant patients. Underlying factors (such as poor compliance and sub-optimal immunosuppression) could have contributed to the organ rejection in these two cases. A causal relationship between H1N1 immunisation and transplant rejection cannot be confirmed at this time. This issue will remain under close review.

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 Agency's Pandemic influenza (H1N1) website.

For information regarding products authorised at a national level, please contact the relevant National Competent Authority (see Regulatory bodies in the European Union for links).

Pandemic information

According to the European Centre for Disease prevention and Control (ECDC) (for latest report click here), a total of 1,333 fatal cases of A/H1N1 influenza in the EU and European Free Trade Association (EFTA) countries and 9,530 in the rest of the world have been reported as of 14 December 2009. While most deaths have to date been in Western Europe there are increasing numbers of deaths being reported from Central and Eastern Europe. The reported cumulative fatal pandemic (H1N1) cases in the world have now passed 10,000 cases. However, because of lack of laboratory confirmation and underreporting, among other factors, this is likely to be a gross underestimation of the true number fatalities associated with the pandemic.

In its Weekly influenza surveillance overview of 11 December 2009, the ECDC concludes that most countries are witnessing medium influenza intensity with only nine reporting high to very high levels. In the majority of countries activity is widespread. Thirteen countries have reported decreasing rates of influenza-like illness for at least the last two weeks. The proportion of influenza-positive sentinel samples continues to decline, but A(H1N1)v still accounts for 99% of all subtyped viruses in sentinel patients. Oseltamivir resistance was found in one percent of influenza pandemic viruses tested in the countries reporting to the **European Influenza Surveillance Network**.

On this topic, see also the report of the World Health Organisation dated 11 December 2009.

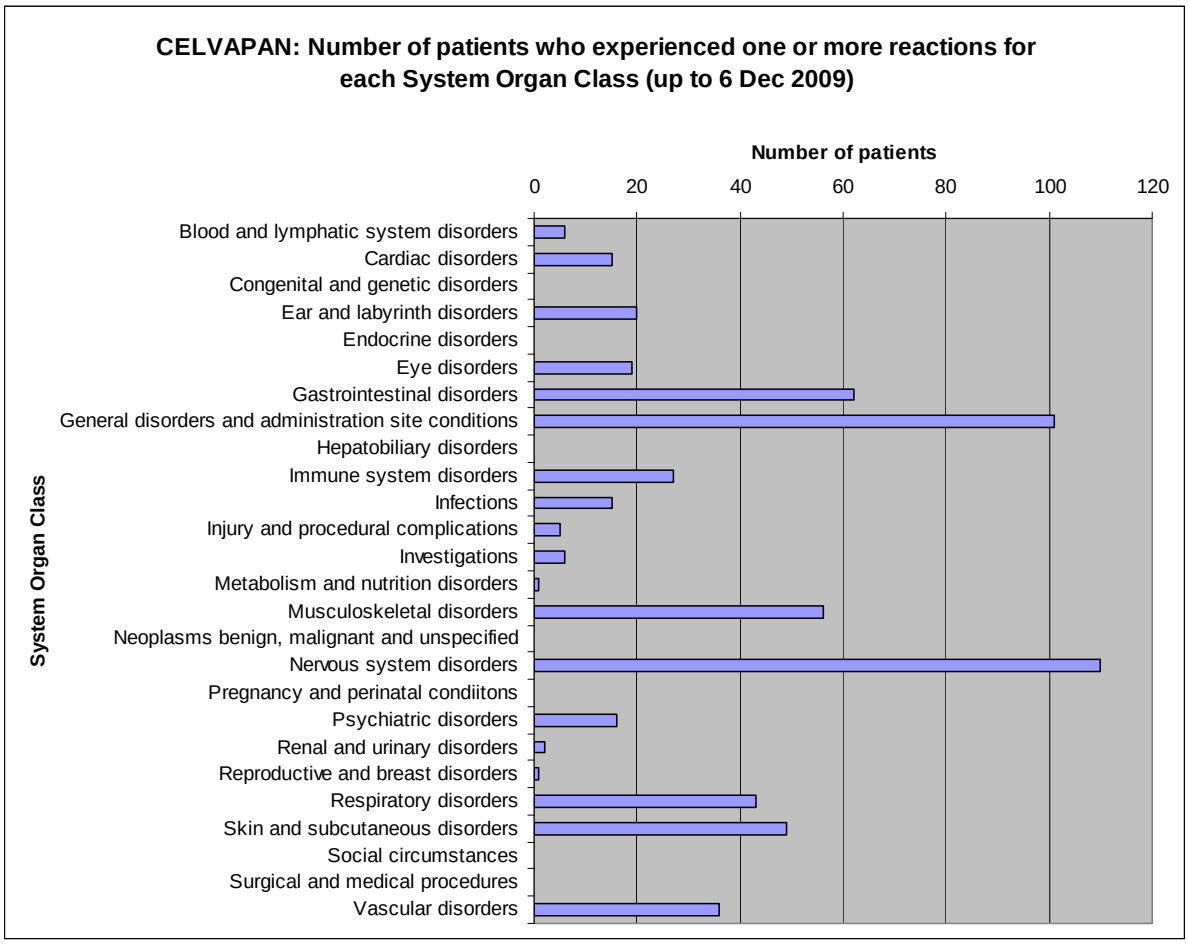
See also the ECDC website for additional information on ECDC.

Overview of centrally authorised vaccines

As of 6 December 2009, a total of 6,101 reports had been received by EudraVigilance since the authorisation of the three centrally-authorised vaccines. This represents an increase of 800 reports compared with the previous update. This increase reflects the increase in the number of vaccinated people. Data available on 14 December 2009 from Member States and from the companies indicate that at least 72.2 million doses have been distributed and at least 26.4 million patients have been vaccinated in the EEA with one of the three centrally-authorised vaccines. From limited information received from 7 countries by 14 December 2009, at least 213,000 pregnant women had been vaccinated.

Celvapan

As of 6 December 2009, a total of 216 reports had been received in EudraVigilance (increase of 25 reports since the previous update). According to company information, a total of 3,399,200 doses had been distributed to EU Member States up to 16 November 2009[1]. It is estimated that at least 438,000 patients have been vaccinated with Celvapan in the EEA.



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

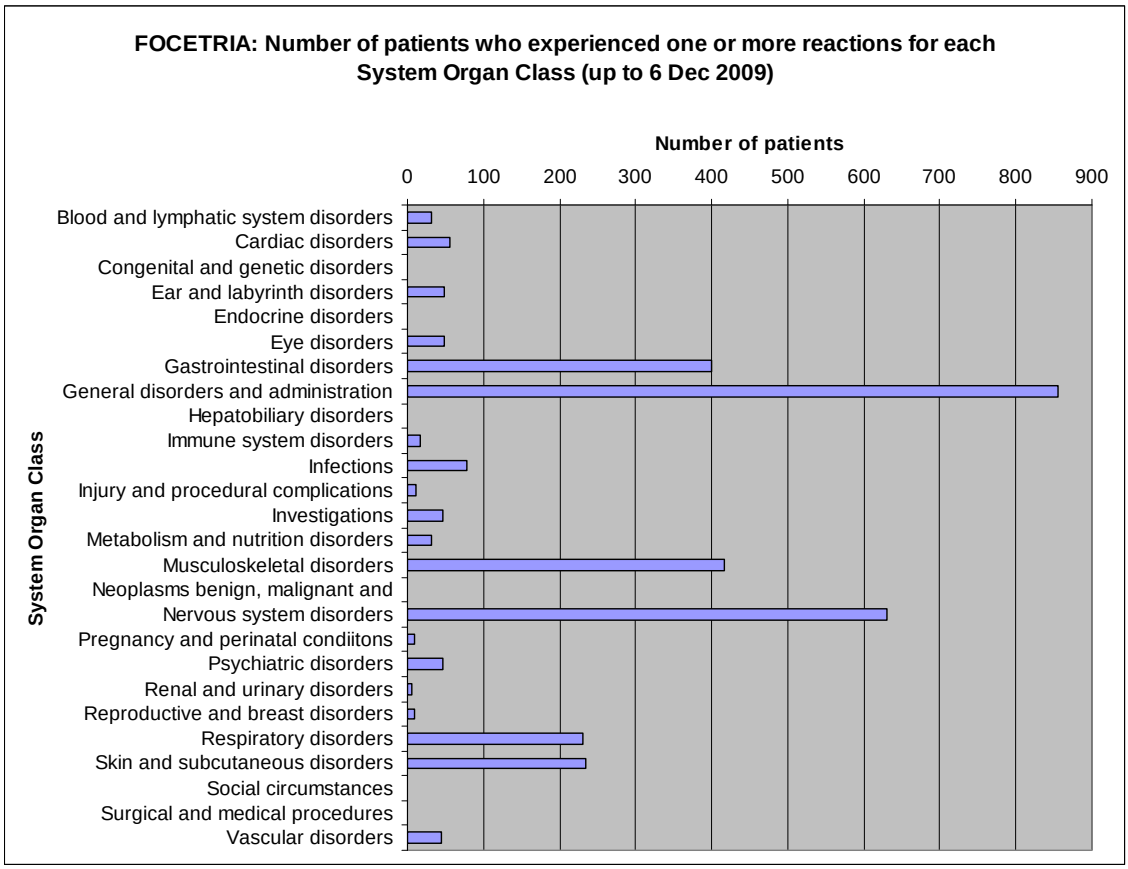
Updated safety information

- The most frequent suspected adverse reactions experienced by patients in each System Organ Class (SOC) since the authorisation of the vaccine are:
  - Nervous system disorders: headache, dizziness, paraesthesia, syncope;
  - General disorders and administration site conditions: pyrexia, malaise, chills, fatigue, feeling hot;
  - Gastrointestinal disorders: nausea, vomiting;
  - Musculoskeletal disorders: arthralgia, myalgia, pain in extremity;
  - Skin and subcutaneous conditions: hyperhydrosis, urticaria, pruritus, rash;
  - Respiratory disorders: dyspnoea, oropharyngeal pain, cough;
  - Vascular disorders: pallor, flushing, hypotension;
  - Immune disorders: hypersensitivity, anaphylactic reaction.
- The most frequently suspected adverse reactions reported in children since authorisation include hypersensitivity, dizziness, headache, vomiting, vision blurred, syncope, urticaria and pallor.
- Since the last update, there has been a new fatal case following administration of Celvapan. This case concerned a 75-year-old male. Little information on this case is currently available. Results of the autopsy have been requested. Since authorisation, a total of two fatal cases have been reported without evidence of an association with Celvapan.
- Since authorisation, 3 cases of circulatory collapse had been received. One case was associated with epilepsy occurring two days after the vaccination and the available information suggest that the two other cases probably experienced vaso-vagal symptoms. All patients recovered.

Focetria

As of 6 December 2009, a total 1,722 reports had been received in EudraVigilance (increase of 152 reports since the previous update). Data available on 14 December 2009 from Member States and from the company[2] indicate that at least 27.3 million doses of Focetria had been distributed in the EEA, and at least 8.5 million individuals had been vaccinated.

[2] As stated by the marketing authorisation holder in the simplified Periodic Safety Update Report (S-PSUR) dated 8 December (data lock point: 30 November 2009).



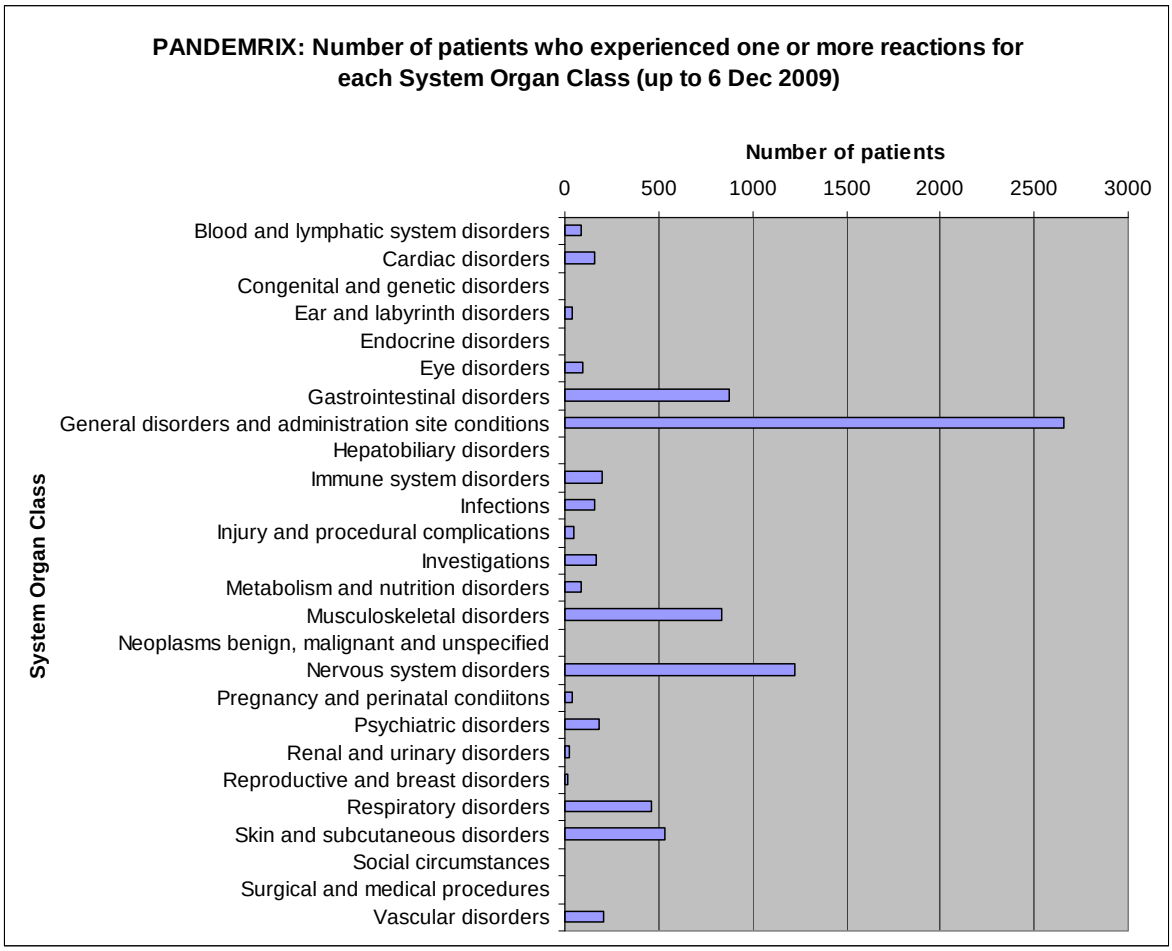
Updated safety information

- The most frequent suspected adverse reactions experienced by patients in each SOC since the authorisation of the vaccine are:
  - General disorders and administration site conditions: pyrexia, fatigue, influenza-like illness, injection site pain, malaise, chills, injection site erythema, injection site swelling;
  - Nervous system disorders: headache, dizziness, paraesthesia, dysgeusia, somnolence;
  - Musculoskeletal disorders: myalgia, pain in extremity, arthralgia, musculoskeletal stiffness;
  - Gastrointestinal disorders: nausea, diarrhoea, vomiting, abdominal pain;
  - Skin and subcutaneous conditions: rash, pruritus, erythema, urticaria, hyperhydrosis;
  - Respiratory disorders: dyspnoea, cough, oropharyngeal pain;
  - Infections: nasopharyngitis, rhinitis.
- The most frequently suspected adverse reactions reported in children since authorisation include pyrexia, headache, cough, nausea, vomiting, abdominal pain, injection site pain, myalgia and influenza-like illness.
- Since authorisation, 12 cases with a fatal outcome have been received. Most are likely to be explained by underlying conditions (e.g. cardiovascular disorders, alcohol abuse, chronic obstructive pulmonary disease, renal insufficiency). In one report with limited information, a 64-year-old patient experienced acute meningo-encephalitis, but the available data do not allow evaluating an association with the vaccine.

- Since the last update, there has been one case of anaphylactic shock in a 1-year-old male with a history of hypersensitivity to chicken-egg-proteins, asthma and atopic eczema, 15 minutes after vaccination. The subject recovered with treatment.
- Since the last update, there has been one case of acute disseminated encephalomyelitis (ADEM) reported in a 67-year-old male, which occurred 5 days after vaccination. The patient was hospitalised and treated with intravenous methylprednisolone and immunoglobulins. Several different viral and bacterial infections have been suggested to lead to ADEM. ADEM has also been temporally reported after various immunisations but there has been no proven association with modern vaccines.
- Since authorisation, there have been two poorly documented cases of encephalitis in patients aged 8 and 64 years old. A link with the vaccine cannot be established based on the available information.

Pandemrix

As of 6 December 2009, a total of 4,163 reports had been received in EudraVigilance (increase of 623 reports since the previous update). Data available on 14 December 2009 from Member States and from the company indicate that at least 42.6 million doses of Pandemrix had been distributed in the EEA. It is estimated that at least 17.4 million individuals have been vaccinated.



Updated safety information

- The most frequent suspected adverse reactions experienced by patients in each SOC since the authorisation of the vaccine are:
  - General disorders and administration site conditions: pyrexia, injection site pain, fatigue, influenza-like illness, malaise, chills, oedema peripheral, pain, injection site swelling, injection site erythema, injection site induration, asthenia;
  - Nervous system disorders: headache, dizziness, paraesthesia, syncope, somnolence, hypoaesthesia, lethargy, convulsions, tremor, loss of consciousness, crying, migraine, presyncope, facial palsy;
  - Gastrointestinal disorders: vomiting, nausea, diarrhoea, abdominal pain;
  - Musculoskeletal disorders: myalgia, pain in extremity, arthralgia, musculoskeletal stiffness, back pain, limb discomfort, muscular weakness, neck pain;
  - Skin and subcutaneous conditions: rash, erythema, hyperhydrosis, urticaria, pruritus;
  - Respiratory disorders: dyspnoea, cough, oropharyngeal pain, rhinorrhoea, asthma, wheezing, bronchospasm, pharyngeal oedema, tachypnoea, epistaxis;
  - Vascular disorders: circulatory collapse, pallor, flushing, hypotension;
  - Immune disorders: anaphylactic reaction, hypersensitivity;
  - Psychiatric disorders: insomnia, listless, restlessness, sleep disorder, tearfulness, nightmare.
- The most frequently suspected adverse reactions reported in children since authorisation include pyrexia, hyperpyrexia, vomiting, injection site pain, headache, fatigue, diarrhoea, cough, abdominal pain, decreased appetite, myalgia, rash and pain in extremity.
- Since authorisation, 57 distinct cases with a fatal outcome have been received. Age ranged from 21 months to 101 years old (median 65 years). Thirty-four (34) patients were 65 years old or above (median 79.5 years); 18 patients were aged between 37 and 64 years (median 50 years); 5 patients were 36 years old or younger (median 17 years). In the majority of cases, pre-existing cardiovascular conditions were reported such as myocardial infarction, arrhythmia, heart failure, coronary heart disease. Other reported underlying conditions that could explain the death included sepsis, pneumonia, renal insufficiency, epilepsy, brain damage, amyotrophic lateral sclerosis.
- Since the last update, there has been one report of injection site necrosis in a 50-year-old female. The patient had a history of morbid obesity and diabetes which may have contributed to the event. Another report concerned a 76-year-old female patient who experienced epidermal necrolysis 3 days after vaccination with Pandemrix. The reporter did not know whether the event was related to the vaccine or to a staphylococcal infection. The subject also had a history of diabetes mellitus and was receiving numerous concomitant medications.
- Since the last update, two new cases of Guillain-Barré syndrome have been received. A 73-year-old male presented with the syndrome 5 days after vaccination with Pandemrix. A 61-year-old male developed the syndrome 10 days after pneumococcal vaccination, and 1 month after administration of both Pandemrix and a seasonal flu vaccine. This person had suffered from gastroenteritis 3 weeks earlier, which may have contributed to the occurrence of Guillain-Barré syndrome. There is no indication that the vaccine contributes to the occurrence of Guillain-Barré syndrome.

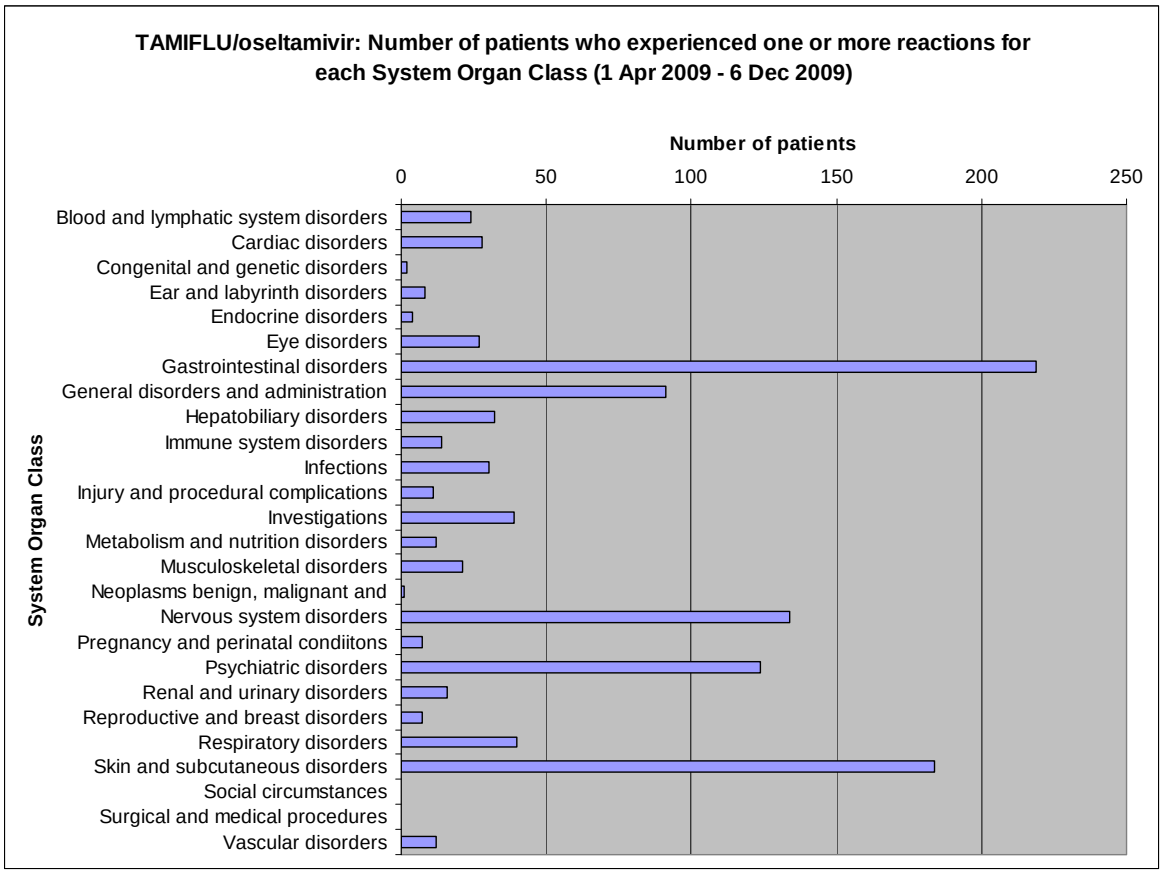
- Since authorisation up to 6 December, a total of 24 distinct cases were received with reported terms corresponding to the high level term (HLT) 'Paralysis and paresis (excluding cranial nerve)'. The following reactions were reported: paresis, monoparesis, hemiparesis, paralysis, paraplegia, diplegia, hemiplegia, monoplegia. Age ranged from 9 to 84 years old; 5 cases occurred in paediatric patients. Time to onset ranged from a few hours to one month after vaccination. The majority (14) of persons had recovered or were recovering at the time of reporting; in remaining persons, the reactions had not yet resolved or the outcome was unknown. Some persons had underlying conditions such as ankylosing spondylitis, tetraplegia, diabetes, epilepsy, lymphoma, multiple sclerosis or migraine. A few cases were suggestive of allergic or severe local injection reactions. A 12-year-old female developed paraplegia 8 hours after vaccination. Further investigation is ongoing for all cases for which the outcome is unknown. It can be concluded that based on the current data there is no evidence that the vaccine caused any of these events.
- In the second weekly update (http://www.ema.europa.eu/pdfs/influenza/79038609en.pdf), it was announced that the European Medicines Agency had been informed of two cases of transplant rejection observed in Sweden following administration of Pandemrix and that investigations were ongoing. As of 13 December 2009, no other case had been reported within the EU despite targeted immunisation of transplant patients. Review of the two Swedish cases has indicated that underlying factors (such as poor compliance and sub-optimal immunosuppression) could have contributed to the organ rejection. Despite the temporal association in these 2 cases, a causal relationship between H1N1 immunisation and transplant rejection cannot be confirmed. This issue will remain under close review. On a purely precautionary basis, Sweden has taken the step to reinforce the recommendation that adequate immunosuppressive treatment in transplanted patients should be ensured before vaccination. Overall, it is concluded on the basis of current data that the product information does not need to be updated regarding the safety of H1N1 vaccinations in organ transplanted patients.
- Since the last update, there has been one report of cerebral infarction in a male newborn who experienced neonatal seizures. His mother had been vaccinated with Pandemrix 4 days before giving birth. It is considered unlikely that the vaccine caused cerebral infarction.

Antiviral medicines

Tamiflu

From 1 April to 6 December 2009, a total number of 753 reports worldwide have been received in EudraVigilance (increase of 19 reports since the previous update). According to information received from the marketing authorisation holder dated 26 November 2009, the patient exposure to oseltamivir is estimated to be approximately 4.3 million patients during the period 1 October 2009 to 31 October 2009 and 13.0 million patients during the period from 1 May 2009 to 31 October 2009[3].

[3] As stated by the marketing authorisation holder in the Pandemic Safety Report dated 26 November 2009.



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, diarrhoea, abdominal pain;
  - SOC Skin and subcutaneous conditions: rash, urticaria, swelling face, pruritis, Stevens-Johnson syndrome;
  - SOC Nervous system disorders: headache, convulsion, paraesthesia, dizziness;
  - SOC Psychiatric disorders: hallucination, confusional state, insomnia, nightmare, delirium;
  - SOC General disorders and administration site conditions: malaise, chest pain, drug interaction, fatigue, oedema peripheral.
- Since 1 April 2009, 146 case reports worldwide have been received by the EudraVigilance system with a fatal outcome following oseltamivir use, including 22 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 could have occurred anyway, in the absence of therapy.