3 February 2010
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Patient Health Protection

# Ninth 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 the 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 of vaccines and antivirals 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 were caused by the medicines. 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 occurring after vaccination.

It should be noted that, due to differences in the numbers of people receiving each vaccine, the number of reports shown for the three different vaccines cannot be used to compare the safety or the benefit-risk balance of the vaccines.

As a single patient may experience several reactions that will be included in a single report, the total number of reactions may not be equal to the total number of patients. In addition, as some patients have received two doses of the vaccines, the total number of doses administered is not necessarily equal to the total number of patients vaccinated.

Reports are collected on a continuous basis in EudraVigilance. EudraVigilance is a database and management system administered 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 by EudraVigilance up to 24 January 2010. 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 presented for the organ systems with the largest number of reports.

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# Key messages

As of 1 February 2010, in the EEA, at least 35.7 million people, including at least 261,000 pregnant women, had been vaccinated with one of the three centrally authorised vaccines (Celvapan, Focetria or Pandemrix). When the information available for the nationally authorised vaccines is included, the total rises to at least 40.2 million people. Some of these have received two doses of a vaccine, but the percentage varies across countries.

The vast majority of the adverse reactions that had been reported as of 24 January 2010 are considered to be non-serious.

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

A cumulative review of all cases of herpes zoster reported to EudraVigilance in temporal association with Celvapan, Focetria or Pandemrix has been performed for this update. A total of 53 cases have been identified and are further discussed below for each vaccine. The risk factors for the re-activation of the varicella-zoster virus are not well understood and the overall background incidence rate in Europe is estimated to be about 4 cases per 1,000 persons per year. Considering that the number of people vaccinated with one of the three vaccines is higher than 35 million, several thousand cases of herpes zoster are expected to coincidently occur shortly after vaccination. There is therefore currently no evidence that the A/H1N1 vaccines could increase the risk of herpes zoster.

For further information on the known adverse reactions included in the authorised product information for the centrally authorised pandemic vaccines (Celvapan, Focetria and Pandemrix) and the antiviral (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

In its weekly influenza surveillance overview of 29 January 2010, the European Centre for Disease Prevention and Control (ECDC) concluded that medium influenza-like illness (ILI) or acute respiratory infection (ARI) activity had been reported in five countries and an increasing trend only in Poland and Slovakia. Widespread geographic activity was only reported in Greece and the United Kingdom (Wales). Of the 840 swabs taken by sentinel physicians, 15% were found to be positive for influenza A virus. Since October 2009, 99% of the subtyped specimens were identified as being the pandemic virus. Among the tested specimens, 2.7% were resistant to oseltamivir. The number of cases of serious ARI continued to decline. Fifty-two percent of new cases were admitted to intensive care units and 37% needed ventilator support.

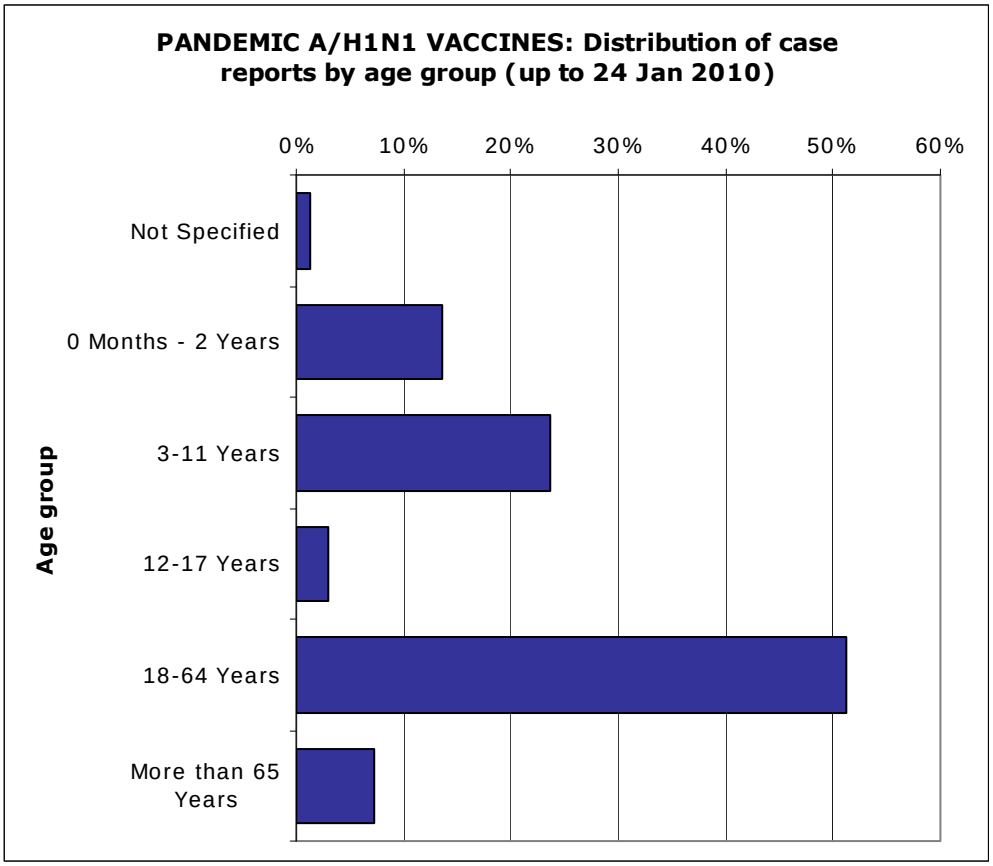
See the ECDC pandemic website, its current risk assessment and its weekly executive update for additional information.

In its weekly update dated 29 January 2010, the World Health Organization stated that, as of 24 January 2010, worldwide more than 209 countries and overseas territories or communities had reported laboratory-confirmed cases of pandemic influenza, including at least 14,711 deaths.

# Overview of centrally authorised vaccines

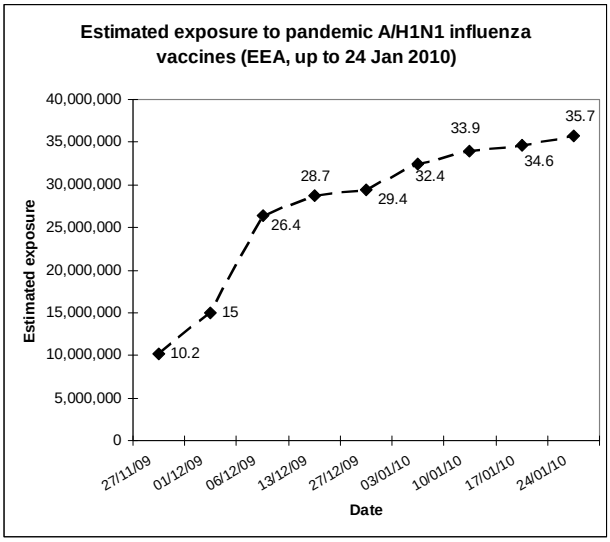
As of 24 January 2010, a total of 12,705 case reports had been received by EudraVigilance since the authorisation of the three centrally authorised vaccines. This represents an increase of 328 reports compared with the previous update, reflecting the increase in the number of people vaccinated.

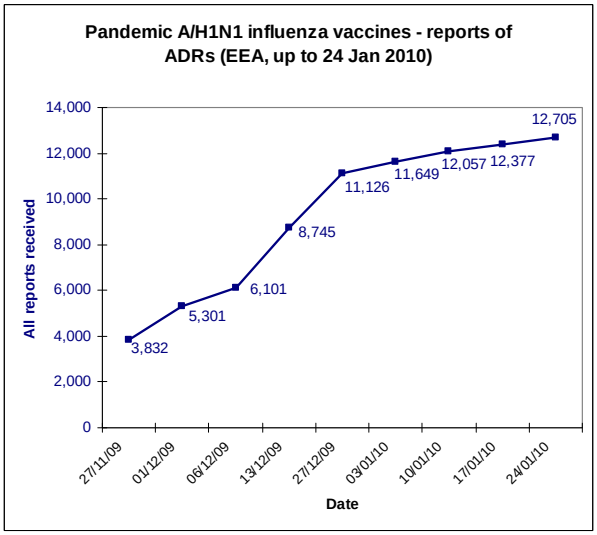
The graph below displays the age distribution of all adverse reaction reports received by EudraVigilance as of 24 January 2010.




Data available on 1 February 2010 from Member States and from the vaccine marketing authorisation holders indicated that at least 127.4 million doses had been distributed and at least 35.7 million patients had been vaccinated with one of the three centrally authorised vaccines in the EEA. From the limited information received from seven EEA countries by 1 February 2010, at least 261,000 pregnant women had been vaccinated. When the information available for the nationally authorised vaccines is included, at least 131.7 million doses had been distributed, with at least 40.2 million people (including at least 298,000 pregnant women) vaccinated in Europe.

The graphs below display, for the three centrally-authorised vaccines, the cumulative numbers of adverse reaction reports received by EudraVigilance over time and the estimated number of people vaccinated, as given in the previous weekly updates. The estimated exposure is derived from information obtained from Member States and is considered to be an underestimate of the true number of people vaccinated. Both curves are reaching a plateau, which indicates a decrease in the number of new adverse reaction reports received by EudraVigilance and in the number of new vaccinations with the three centrally-authorised vaccines.

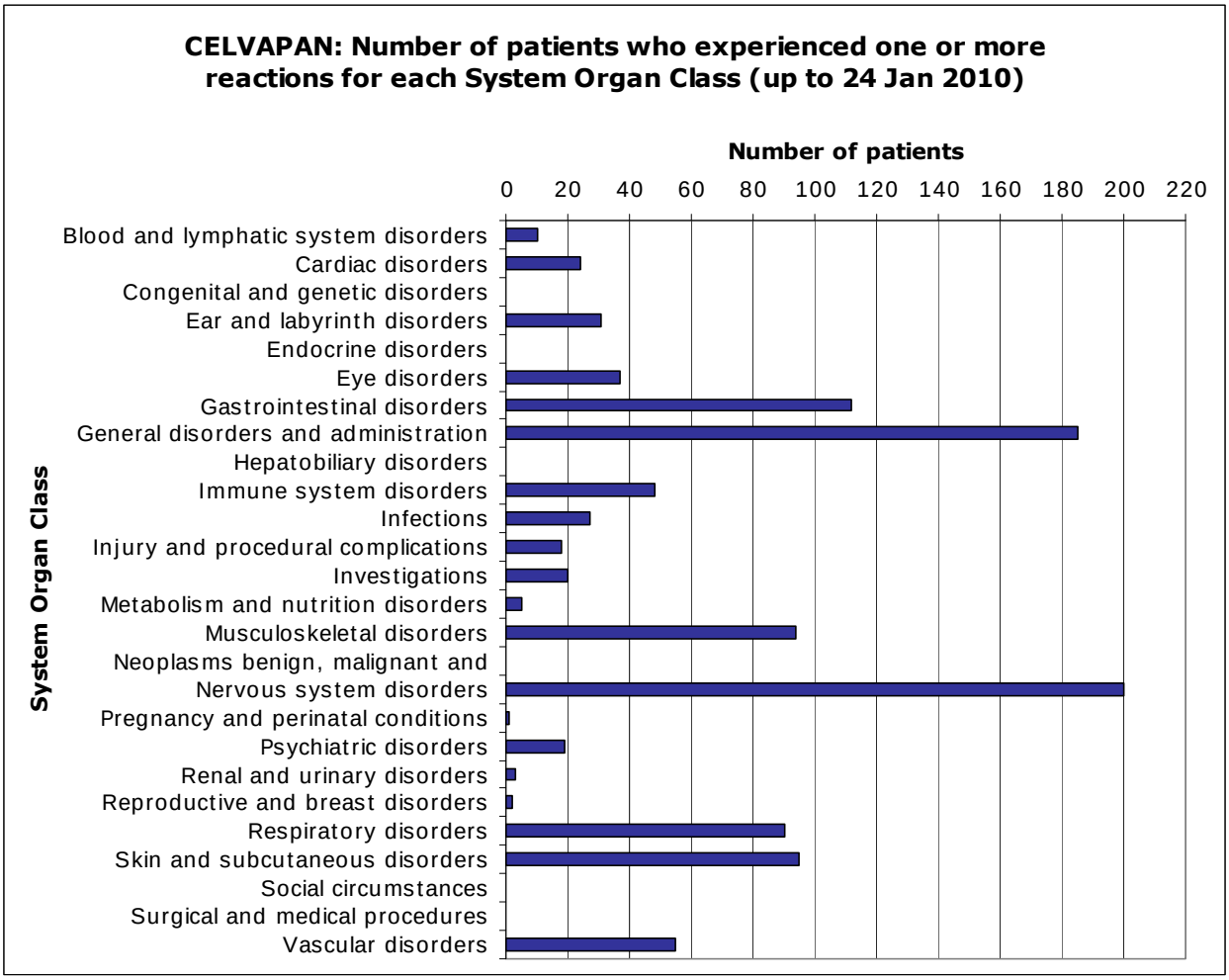



A list of specific topics discussed in previous updates is included in the appendix.

## *Celvapan*

As of 24 January 2010, a total of 432 reports had been received by EudraVigilance (an increase of 31 reports since the previous update). According to the information provided by the company[1] and Member States, at least 7.5 million doses had been distributed to EEA countries up to 11 January 2010. It is estimated that at least 571,000 patients have been vaccinated with Celvapan in the EEA.




## Distribution of adverse reactions by system organ class

- In reports received from the EEA, the most frequently reported suspected adverse reactions in each system organ class (SOC) experienced by patients since the authorisation of the vaccine were:
  - Nervous-system disorders: headache, dizziness, syncope, paraesthesia, hypoaesthesia, lethargy;
  - General disorders and administration-site conditions: pyrexia, malaise, chills, fatigue, asthenia, influenza-like illness, feeling hot, injection-site pain, chest discomfort;
  - Gastrointestinal disorders: nausea, vomiting, diarrhoea, abdominal pain, oral paraesthesia;
  - Musculoskeletal disorders: myalgia, arthralgia, pain in extremity, muscular weakness;

[1] As stated by the marketing authorisation holder in the periodic safety update report dated 22 January 2010.

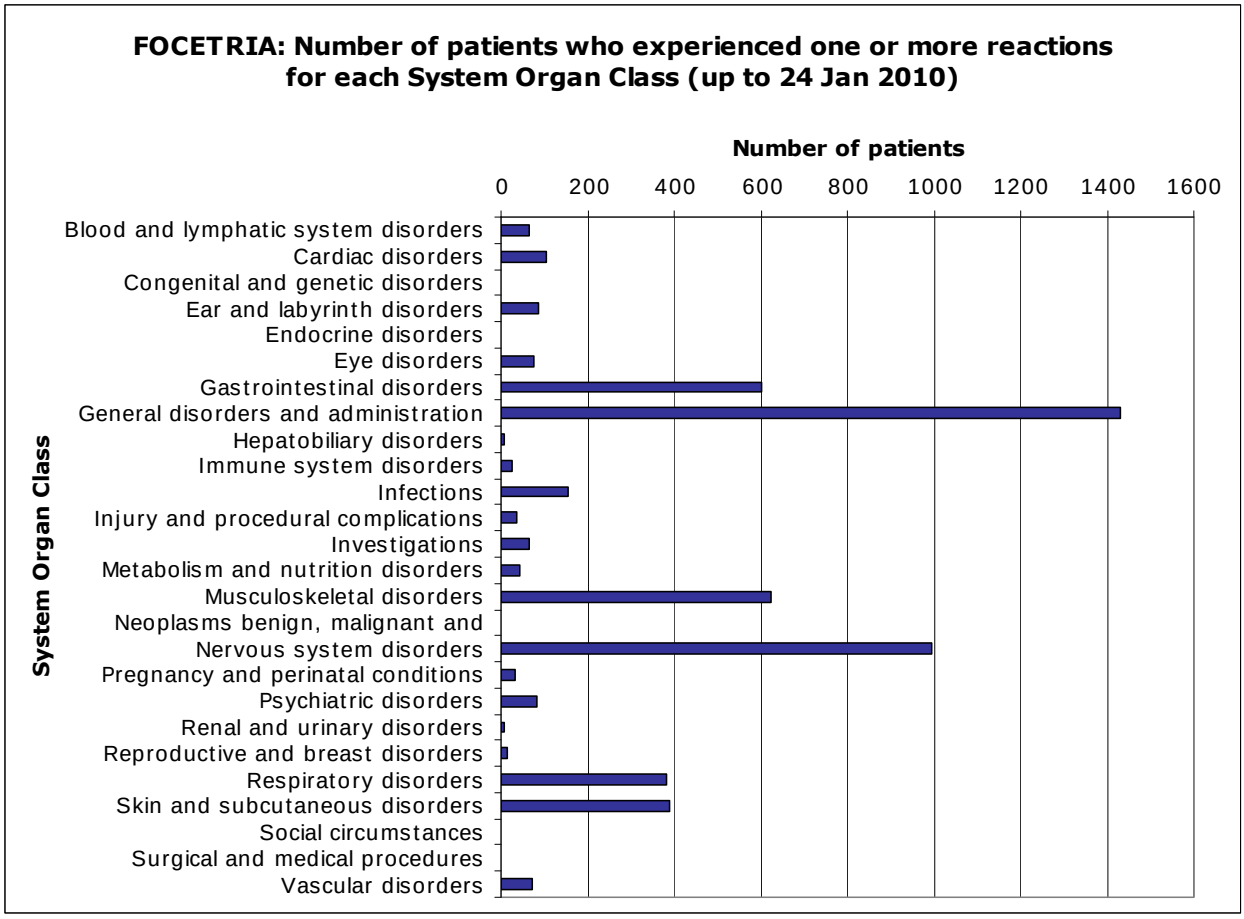
- Skin and subcutaneous conditions: hyperhidrosis, pruritus, urticaria, rash, erythema;
- Respiratory disorders: cough, oropharyngeal pain, dyspnoea;
- Vascular disorders: pallor, flushing, hypotension;
- Immune disorders: hypersensitivity, anaphylactic reaction, anaphylactoid reaction;
- Eye disorders: vision blurred;
- Ear and labyrinth disorders: vertigo;
- Infections: rhinitis;
- Cardiac disorders: tachycardia;
- Investigations: body temperature increased;
- Psychiatric disorders: sleep disorders;
- Injury and procedural complications: medication error.

## Updated safety information

- The most frequently reported suspected adverse reactions in children since authorisation included hypersensitivity, syncope, vomiting, pyrexia, dizziness, pallor, nausea, headache, rash, medication error, cough, vision blurred, chills, hyperhidrosis, malaise and urticaria.
- Since the last update, no fatal cases have been reported in people vaccinated with Celvapan.
- Since authorisation, two adverse reaction reports of herpes zoster have been received in temporal association with Celvapan. A herpetic eruption was diagnosed on the arm of a 39-year-old patient from the shoulder to the wrist. The patient recovered six days later. The other case occurred four days after the vaccination but is not documented. These two cases do not suggest an association between the vaccine and the occurrence of herpes zoster.

### *Focetria*

As of 24 January 2010, a total of 2,837 reports had been received by EudraVigilance (an increase of 30 reports since the previous update). Data available on 1 February 2010 from Member States and from the company[2] indicated that at least 37 million doses of Focetria had been distributed in the EEA, and at least 7.7 million patients had been vaccinated.




## Distribution of adverse reactions by system organ class

- In reports received from the EEA, the most frequently reported suspected adverse reactions in each SOC experienced by patients since the authorisation of the vaccine were:
  - General disorders and administration-site conditions: pyrexia, fatigue, injection-site pain, influenza-like illness, malaise, chills, injection-site erythema, hyperpyrexia, injection-site swelling, injection-site induration, chest pain, asthenia, injection-site pruritus, pain, feeling cold, injection-site haematoma, feeling hot, injection-site warmth, oedema peripheral;
  - Nervous-system disorders: headache, dizziness, paraesthesia, somnolence, tremor, syncope, dysgeusia, hypoaesthesia, presyncope, convulsion, Guillain-Barré syndrome, migraine;
  - Musculoskeletal disorders: myalgia, pain in extremity, arthralgia, musculoskeletal stiffness, muscular weakness, neck pain, muscle spasms, musculoskeletal pain, back pain, sensation of heaviness, rheumatoid arthritis;

[2] As stated by the marketing-authorisation holder in the periodic safety update report dated 6 January 2010.

- Gastrointestinal disorders: nausea, diarrhoea, vomiting, abdominal pain, abdominal discomfort, upper abdominal pain, dyspepsia;
- Skin and subcutaneous conditions: rash, pruritus, urticaria, erythema, hyperhidrosis, rash pruritic, dermatitis allergic, angioedema, swelling face, rash generalised, eczema;
- Respiratory disorders: cough, dyspnoea, oropharyngeal pain, asthma, bronchospasm, dysphonia, throat irritation;
- Infections: rhinitis, nasopharyngitis, pneumonia, influenza, pharyngitis, herpes zoster;
- Cardiac disorders: palpitations, tachycardia, atrial fibrillation, cyanosis;
- Ear and labyrinth disorders: vertigo, tinnitus, ear pain;
- Psychiatric disorders: listlessness, insomnia, nightmare, restlessness, tearfulness;
- Eye disorders: eyelid oedema, visual impairment, eye irritation, eye swelling, eye pain;
- Vascular disorders: hypotension, flushing, hypertension, pallor, haematoma, peripheral coldness;
- Investigations: body temperature increased, blood pressure increased, heart rate increased;
- Blood and lymphatic disorders: lymphadenopathy;
- Metabolism and nutrition disorders: decreased appetite;
- Immune system disorders: hypersensitivity.

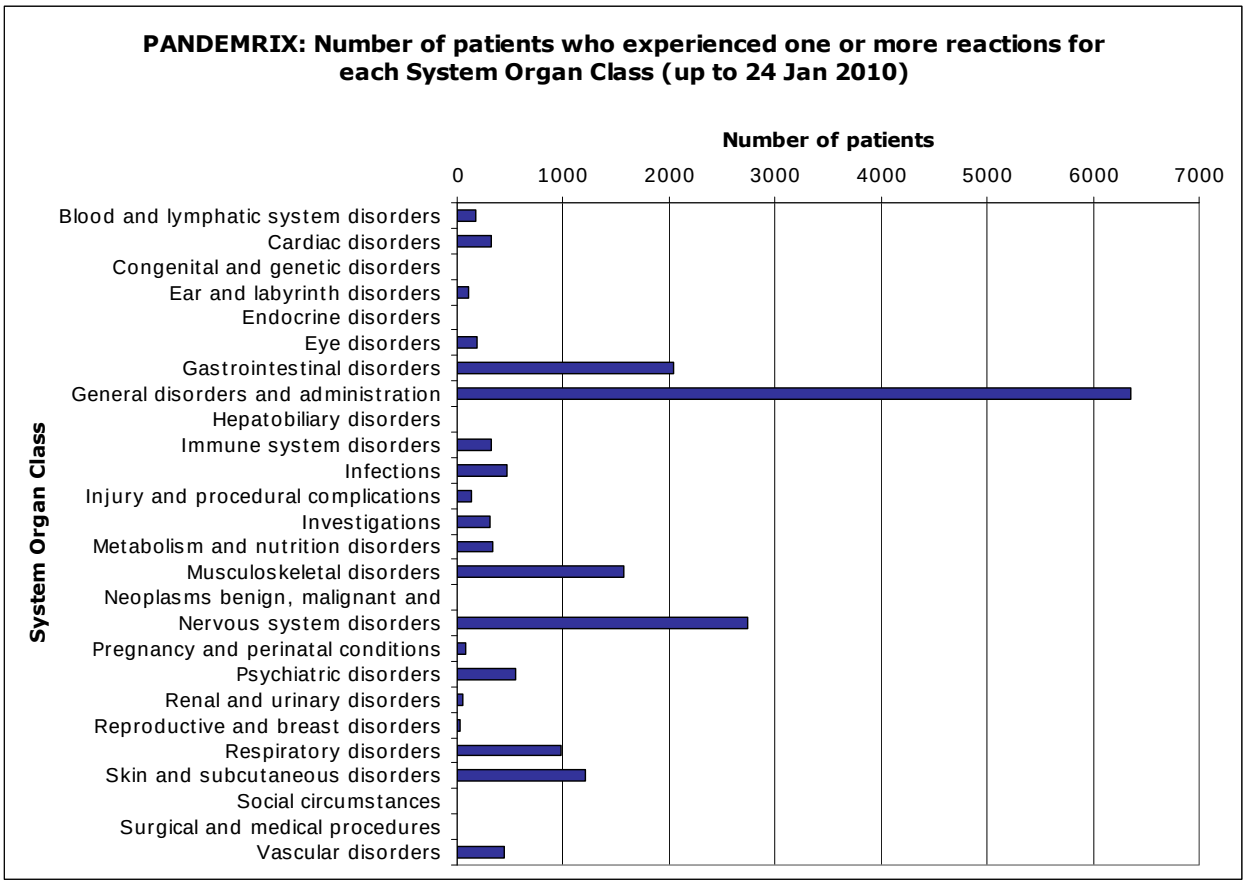
## Updated safety information

- The most frequently reported suspected adverse reactions in children since authorisation included pyrexia, headache, hyperpyrexia, vomiting, cough, nausea, abdominal pain, diarrhoea, injection-site pain, myalgia, fatigue, influenza-like illness, rash, dyspnoea, malaise, convulsion, pain in extremity and urticaria.
- Since the last update, one fatal case has been received, describing a 79-year-old man whose medical conditions included hypertension and diabetes mellitus. He died two days after the vaccination due to heart failure. This report originated from a non-EEA country.
- Since authorisation, seven cases of herpes zoster reported in association with the use of Focetria have been received by EudraVigilance. They concerned five women and two men with ages ranging from 22 to 77 years. The delay after vaccination was one day in three cases, three days in two cases, and five and seven days in one case each. One patient with a medical history of systemic lupus erythematosus and chronic lymphocytic leukaemia has recovered with post-herpetic neuralgia. The other patients were recovering at the time of the report. Based on an overall background rate of about 4 cases of herpes zoster per 1,000 persons per year, several hundred cases are expected to coincidently occur within one week after the Focetria vaccination, and there is currently no evidence that Focetria increases the risk of occurrence of herpes zoster.
- Since authorisation, five reports of bullous lesions on the skin have been received by EudraVigilance. They concern three cases reported as ‘blister’, one case of bullous dermatitis and one case of toxic epidermal necrolysis (TEN). The cases of blister and bullous dermatitis occurred within two days of vaccination and were assessed as being possibly related to Focetria. One case of blister was observed in the context of cellulitis. The diagnosis of TEN in one patient has not been ascertained but could possibly be explained by concomitant drugs that are known to be associated

with this reaction. Generalised skin reactions and allergic reactions are mentioned in the product information as reactions that have been observed during the post-marketing surveillance of Focetria. Additional reports of bullous reactions will be evaluated and this issue will be closely monitored.

### *Pandemrix*

As of 24 January 2010, a total of 9,449 reports had been received by EudraVigilance (an increase of 270 reports since the previous update). Data available on 1 February 2009 from Member States and from the company[3] indicate that at least 82.7 million doses of Pandemrix had been distributed in the EEA. It is estimated that at least 26 million patients have been vaccinated.




## Distribution of adverse reactions by system organ class

- In reports received from the EEA, the most frequently reported suspected adverse reactions in each SOC experienced by patients since the authorisation of the vaccine were:
  - General disorders and administration-site conditions: pyrexia, hyperpyrexia, injection-site pain, fatigue, influenza-like illness, malaise, chills, injection-site swelling, injection site erythema, pain, oedema peripheral, asthenia, injection-site induration, injection-site inflammation, chest pain, feeling hot, chest discomfort;
  - Nervous-system disorders: headache, dizziness, paraesthesia, somnolence, syncope, crying, hypoaesthesia, febrile convulsion, lethargy, convulsion, tremor, loss of consciousness, poor quality sleep, presyncope, facial palsy, hypersomnia, hypotonia;
  - Gastrointestinal disorders: vomiting, nausea, diarrhoea, abdominal pain, upper abdominal pain, paraesthesia oral, lip swelling, dry mouth, swollen tongue, hypoaesthesia oral, abdominal discomfort, dysphagia, lower abdominal pain;

[3] As stated by the marketing-authorisation holder in the periodic safety update report dated 15 January 2009.

- Musculoskeletal disorders: myalgia, pain in extremity, arthralgia, musculoskeletal stiffness, muscular weakness, back pain, limb discomfort, musculoskeletal pain, neck pain, muscle spasms, arthritis;
- Skin and subcutaneous conditions: rash, erythema, urticaria, hyperhidrosis, pruritus, rash generalised, angioedema, swelling face, cold sweat, rash erythematous, dermatitis allergic, rash macular, rash pruritic, facial hypoaesthesia, petechiae, pruritus generalised, eczema, skin reaction, vesicular rash;
- Respiratory disorders: cough, dyspnoea, oropharyngeal pain, asthma, rhinorrhoea, wheezing, epistaxis, tachypnoea, pharyngeal oedema, throat tightness, bronchospasm, sneezing, dysphonia, productive cough, respiratory failure, pulmonary embolism, respiratory distress, stridor;
- Psychiatric disorders: listlessness, insomnia, tearfulness, sleep disorder, restlessness, nightmare, confusional state, hallucination;
- Infections: rhinitis, nasopharyngitis, pneumonia, influenza, herpes zoster, swine influenza, cellulitis, ear infection, bronchitis, respiratory tract infection;
- Vascular disorders: pallor, circulatory collapse, hypotension, flushing, hypertension, hot flush, peripheral coldness;
- Metabolism and nutrition disorders: decreased appetite, oligodipsia, dehydration;
- Cardiac disorders: tachycardia, palpitations, cyanosis, myocardial infarction, cardiac failure, atrial fibrillation, cardiac arrest, bradycardia;
- Immune disorders: hypersensitivity, anaphylactic reaction, anaphylactic shock, anaphylactoid reaction;
- Investigations: body temperature increased, blood pressure decreased, blood pressure increased, heart rate increased, heart rate decreased;
- Eye disorders: eye swelling, eye pain, vision blurred, ocular hyperaemia, eyelid oedema, diplopia, conjunctivitis;
- Blood and lymphatic system disorders: lymphadenopathy, thrombocytopenia;
- Injury and procedural disorders: vaccination failure, medication error, contusion;
- Ear and labyrinth disorders: vertigo, tinnitus, ear pain.

## Updated safety information

- Since the last update, seven fatal cases from the EEA have been received. Two patients aged 83 and 90 years died of pneumonia, two patients aged 79 and 71 years died of cardiac causes (cardiopulmonary arrest and acute heart disease), a 81-year-old patient died from an unexplained cause the same day as the vaccination, a 43-year-old patient died from suspected ruptured oesophageal varices and a 32-year-old patient died from suspected drug intoxication four days after the vaccination. There is no evidence of a causal association between these deaths and Pandemrix.
- The most frequently reported suspected adverse reactions in children since authorisation were pyrexia, hyperpyrexia, vomiting, injection-site pain, diarrhoea, headache, cough, fatigue, rash, decreased appetite, abdominal pain, nausea, malaise, somnolence, listlessness, injection-site

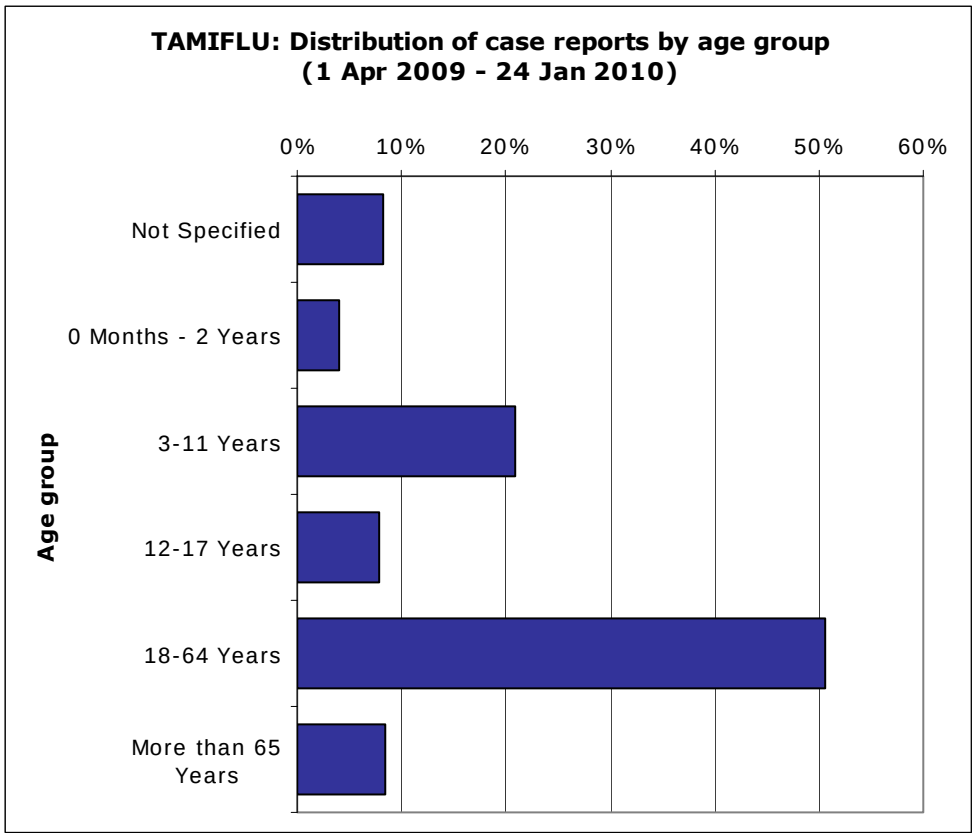
erythema, crying, injection site swelling, pallor, dyspnoea, influenza-like illness, pain in extremity, myalgia, syncope and tearfulness.

- The safety profile of Pandemrix has been reassessed in the context of the third periodic safety update report submitted by the company. The assessment concluded that no new risks have been identified in any age group and that the benefit-risk balance remains favourable. Additional information was requested from the company regarding the following reported adverse events: cyanosis, ear pain and tinnitus, oral hypoaesthesia and paraesthesia, hypoaesthesia, administration and medication errors, arthropathies, paralysis and paresis, bronchospasm, and cough.
- Since authorisation, 44 cases of herpes zoster have been reported from the EEA in association with Pandemrix vaccination, with a median age of 59 years. In five cases, Pandemrix had been administered concomitantly with a seasonal influenza vaccine. The time to onset was from zero to six days in 29 cases, seven to eight days in five cases, nine to 25 days in eight cases, and unknown in two cases. In many cases, a medical condition may have increased the risk of developing herpes zoster, such as previous herpes infection, an immune system disorder, HIV infection, immunosuppressant treatment or a haematological cancer. No risk factors were identified in a third of the cases, which occurred with a short temporal association with the vaccine. The issue of herpes zoster was assessed in the context of the third periodic safety update report submitted by the company. It was concluded that there is no sign of a causal association with Pandemrix. Several thousand cases would be expected to occur coincidently within one month of vaccination.
- Three cases of severe pain followed by nerve damage and muscle atrophy affecting the shoulder were reported shortly after vaccination with Pandemrix in patients aged 32, 47 and 54 years. A diagnosis of neuralgic amyotrophy was made. Neuralgic amyotrophy is a rare auto-immune disorder whose cause is generally unknown. Since only three cases were reported, a causal association with Pandemrix cannot be established. The issue will be kept under review.

# Antiviral medicines

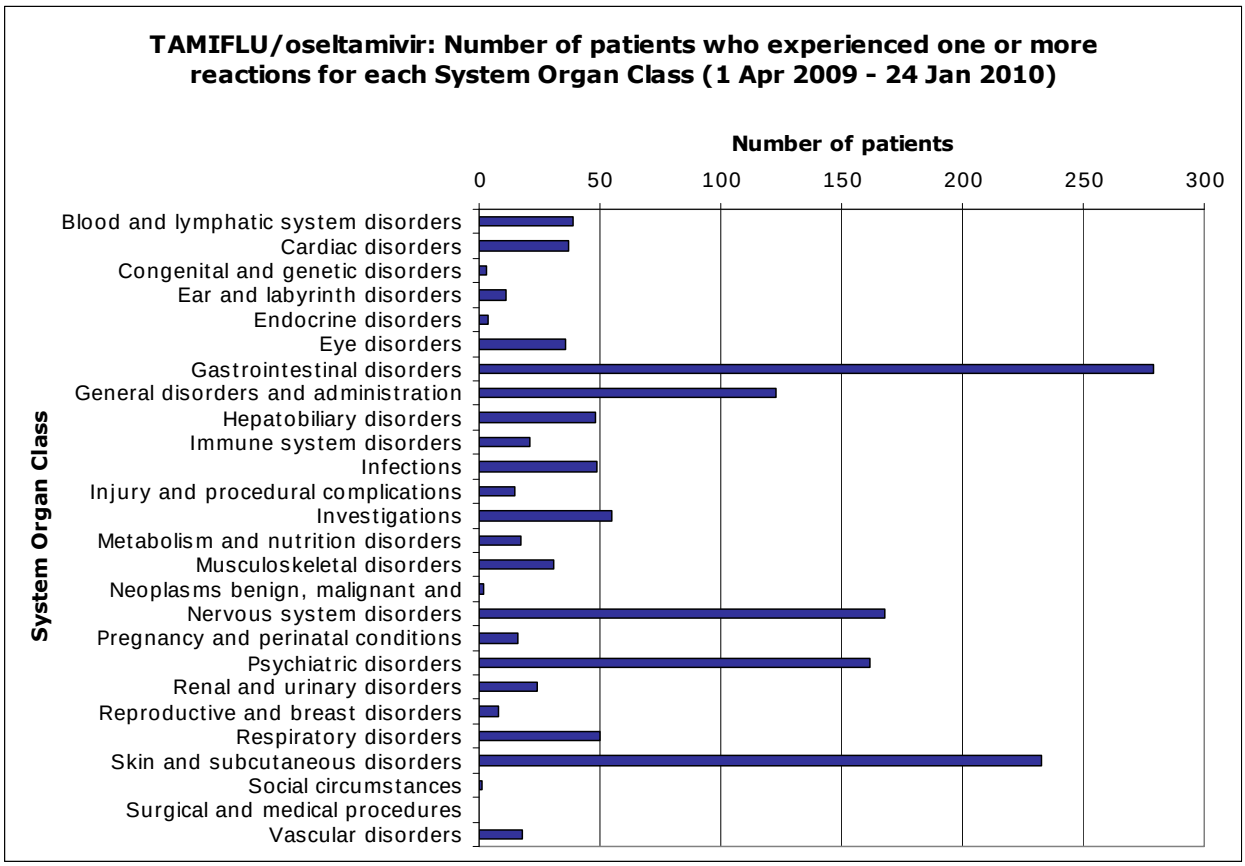
## *Tamiflu (oseltamivir)*

From 1 April to 24 January 2010, a total of 969 reports worldwide were received by EudraVigilance (an increase of 22 reports since the previous update). The graph below displays the age distribution of patients experiencing an adverse reaction reported to EudraVigilance.




According to information received from the marketing authorisation holder dated 23 December 2009, exposure to Tamiflu is estimated to be at least 16.3 million patients during the pandemic period of 1 May to 30 November 2009[4].

[4] As stated by the marketing-authorisation holder in the pandemic safety report dated 23 December 2009.




## Distribution of adverse reactions by system organ class

- The adverse reaction reports received from the EEA are consistent with the safety profile described in the product information. The most frequently reported suspected adverse reactions experienced by patients in each SOC were as follows:
  - Gastrointestinal disorders: vomiting, nausea, diarrhoea, abdominal pain, upper abdominal pain, mouth ulceration, lip swelling, swollen tongue, haematemesis, pancreatitis, pancreatitis acute;
  - Skin and subcutaneous conditions: rash, rash generalised, urticaria, swelling face, erythema, Stevens-Johnson syndrome, pruritus, rash erythematous, rash pruritic, rash macular, angioedema;
  - Nervous-system disorders: headache, convulsion, paraesthesia, dizziness, tremor, syncope, cardiovascular accident, nystagmus, epilepsy, burning sensation, dysgeusia, somnolence;
  - Psychiatric disorders: hallucination, confusional state, nightmare, insomnia, anxiety, delirium, hallucination visual, disorientation, agitation, panic attack, abnormal behaviour, depressed mood, mental disorder, psychotic disorder;
  - General disorders and administration-site conditions: malaise, death, pyrexia, chest pain, oedema peripheral, drug interaction, fatigue, influenza-like illness, condition aggravated, general physical health deterioration, face oedema, pain, drug ineffective, gait disturbance;
  - Investigations: liver function test abnormal, international normalised ratio increased, hepatic enzyme increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, prothrombin time prolonged;

- Respiratory disorders: epistaxis, dyspnoea, chronic obstructive pulmonary disease;
- Infections: pathogen resistance, influenza, lower respiratory tract infection, pneumonia;
- Hepatobiliary disorders: hepatitis, hepatic failure, acute hepatic failure, hepatotoxicity.

## Updated safety information

- Since the last update, nine new worldwide reports of adverse events with a fatal outcome occurring following oseltamivir use have been received by EudraVigilance. The causes of death were pneumonia, meningitis or influenza in six cases; haemorrhagic shock considered not to be related to oseltamivir in one case; and cardiac arrest in a context of diarrhoea, vomiting, acute renal failure and hyperglycaemia in one case. In one case, the cause of death was unknown.
- Additional information was received regarding two previously reported cases of death. In one case, sudden death occurred after severe respiratory depression episodes; acute myocarditis and pneumonitis were also suspected as being causes of death. In the second case, the death was considered to be related to peripartum cardiomyopathy. Morbid obesity, pneumonia and drug abuse were reported as contributing to this second death.
- The most frequently reported suspected adverse reactions reported in children since the beginning of the pandemic in April 2009 were vomiting, rash, hallucination, confusional state, nightmare, epistaxis, headache, convulsion, urticaria, diarrhoea, nausea and abdominal pain.
- A total of 37 cases of hypotension have been reported to EudraVigilance in temporal association with the use of oseltamivir. In 22 of these cases, shock was also reported. In 16 cases, concomitant treatments or clinical conditions (such as hepatic failure, multi-organ failure, dehydration, Stevens-Johnson syndrome, fever, nausea, vomiting or tubular necrosis) could provide an alternative explanation. No alternative explanations have been identified for the other cases. A further evaluation of this issue will be carried out.

# Appendix

## Specific topics discussed for H1N1 vaccines in previous updates

| SOC | Topic | Update number | | |
|---|---|---|---|---|
| | | Celvapan | Focetria | Pandemrix |
| **Blood and lymphatic system disorders** | Haematopoietic cytopenias | | | 8 |
| | Idiopathic thrombocytopenic purpura (ITP) | | | 4, 6 |
| | Leucocytosis, lymphocytosis | | | 8 |
| | Thrombocytopenia | | 6 | 6 |
| **Cardiac disorders** | Cardiovascular accidents | | 5 | |
| **Ear and labyrinth disorders** | Sudden hearing loss | | | 4 |
| **Eye disorders** | Eye disorders | 4, 7 | 7 | 7 |
| | Photophobia | | | 7 |
| **Gastrointestinal disorders** | Acute pancreatitis | 7 | | |
| | Necrotising oesophagitis and necrotising stomatitis | | | 6 |
| **General disorders and administration site conditions** | Fever, local reaction and drowsiness following 2nd dose in children 6-35 months old | | | 1 |
| | Injection site necrosis | | | 3 |
| **Immune system disorders** | Anaphylactic reactions in children | | | 1 |
| | Anaphylactic shock | | 2, 3 | 2 |
| | Anaphylaxis, angioedema, hypersensitivity | 2 | | |
| | Delayed hypersensitivity reaction type IV | | | 4 |
| | Serum sickness | | | 6 |
| | Transplant rejection | | | 1, 2, 3 |

| SOC | Topic | Update number | | |
|---|---|---|---|---|
| | | Celvapan | Focetria | Pandemrix |
| **Injury, poisoning and procedural complications** | Medication error | 7 | | 7 |
| **Nervous system disorders** | Acute disseminated encephalomyelitis (ADEM) | | 2, 3 | |
| | Cerebral haemorrhage | | 1 | |
| | Cerebral infarction | | | 3 |
| | Encephalitis | | 3, 5 | |
| | Facial palsy | | 4, 8 | 7 |
| | Facial paresis | 8 | 8 | |
| | Guillain-Barré syndrome | 4, 5 | 2, 4, 5 | 1, 3, 4, 5, 6 |
| | Multiple sclerosis | | 5 | 5 |
| | Neuritis, polyneuritis, polyradiculoneuritis, peripheral neuropathy, polyneuropathy | | | 6 |
| | Paraesthesia | 2 | | |
| | Paralysis and paresis | 7 | 8 | 3 |
| | Seizures | | 8 | |
| | Seizures with fatal outcome | | | 4 |
| **Pregnancy, puerperium and perinatal conditions** | Intra-uterine death | | 4 | |
| | Pregnancy-related events | | 2 | 1, 2 |
| **Skin and subcutaneous tissue disorders** | Bullous dermatitis | | | 8 |
| | Erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) | | | 3, 6 |
| | Leukocytoclastic vasculitis | | 5 | |
| | Photosensitivity reaction | | | 2 |
| | Systemic lupus erythematosus rash | | | 8 |

| SOC | Topic | Update number | | |
|---|---|---|---|---|
| | | Celvapan | Focetria | Pandemrix |
| **Vascular disorders** | Circulatory collapse | 3 | | |
| | Vasculitis | | | 6 |

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