EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Patient Health Protection

Twelfth pandemic pharmacovigilance weekly update

This report summarises the adverse drug reactions reported after the use of the centrally authorised pandemic vaccines Arepanrix, Celvapan, Focetria and Pandemrix and the antiviral Tamiflu. 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.

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.

Due to different number of people receiving each vaccine, the number of reports for the four 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 in EudraVigilance, 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. EudraVigilance allows the transfer of reports from national regulatory agencies and marketing authorisation holders to the 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 14 February 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

On 19 February 2010, the European Medicines Agency announced that the Agency's Committee for Medicinal Products for Human Use (CHMP) has recommended the granting of a conditional marketing authorisation for Humenza, from Sanofi Pasteur. There are currently five pandemic vaccines recommended for use by the Committee (Arepanrix, Celvapan, Focetria, Humenza and Pandemrix). Four of them have received an EU-wide authorisation from the European Commission (Arepanrix, Celvapan, Focetria and Pandemrix) and three are currently marketed in the EEA (Celvapan, Focetria and Pandemrix).

As of 22 February 2010, in the EEA, at least 36.5 million people, including at least 322,000 pregnant women, had been vaccinated with one of the three centrally authorised vaccines marketed in the EEA, Celvapan, Focetria or Pandemrix. When the information available for the nationally authorised vaccines is included, the total rises to at least 42.5 million people. Some of these have received two doses of a vaccine, but the percentage varies between countries.

The vast majority of the adverse reactions that had been reported as of 14 February 2010 are considered to be non-serious.

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

The Committee also reviewed further results from clinical studies and post-marketing experience for Celvapan, Focetria and Pandemrix. The data confirmed the safety profile of the vaccines and showed no unexpected serious safety issue. For Celvapan and Focetria the Committee recommended changes to the product information to include additional information on the vaccines' safety.

For further information on the known adverse reactions included in the authorised product information for the centrally authorised pandemic vaccines Arepanrix, 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).

This twelfth pandemic update is the last update to be published weekly. Subsequently pandemic pharmacovigilance updates will be published every two weeks. The thirteenth update will be published by the Agency on 10 March 2010.

Pandemic information

In its weekly influenza surveillance overview of 19 February 2010, the European Centre for Disease Prevention and Control (ECDC) concluded that the 2009 influenza A(H1N1) pandemic is well past its winter peak in EU/EEA countries. In seven countries (the majority of which are in Eastern Europe), local or regional transmission of the pandemic virus continues at low to medium intensity. Sporadic transmission of the pandemic virus was reported in the majority of the countries.

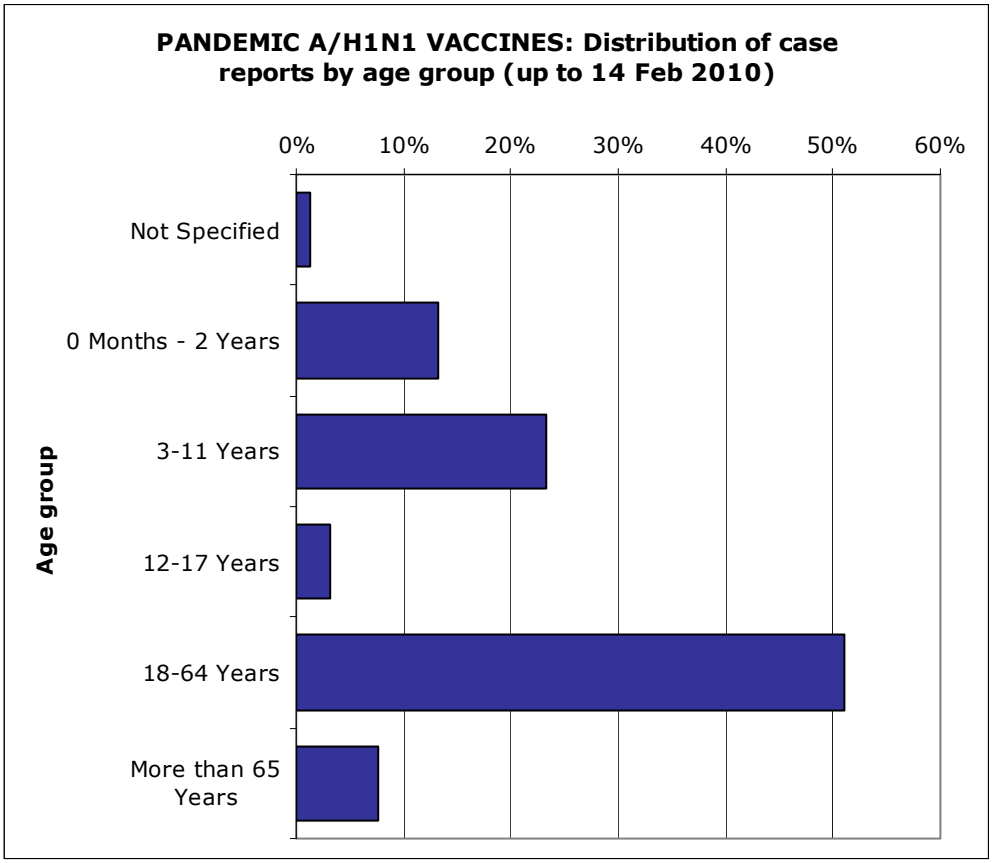
The number of confirmed fatal cases announced by EU/EEA Member States on their official websites as due to the pandemic has reached 2,678 by 15 February 2010. Click here for the breakdown by country.

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

In its weekly update dated 19 February 2010, the World Health Organization stated that, as of 14 February 2010, worldwide more than 212 countries and overseas territories or communities have reported laboratory confirmed cases of pandemic influenza H1N1 2009, including at least 15,921 deaths.

Overview of centrally authorised vaccines

As of 14 February 2010, a total of 13,354 case reports had been received by EudraVigilance since the authorisation of the three centrally authorised vaccines marketed in the EEA. This represents an increase of 224 reports compared with the previous update. The graph below displays the age distribution of all the reports received by EudraVigilance.



Data available on 22 February 2010 from Member States and from the vaccine marketing authorisation holders indicate that at least 129.2 million doses had been distributed and at least 36.5 million patients had been vaccinated with one of the three vaccines marketed in the EEA. From the limited information received from seven countries, at least 322,000 pregnant women had been vaccinated. When the information available for the nationally authorised vaccines is included, at least 133.5 million doses had been distributed, with at least 42.5 million people (including at least 361,000 pregnant women) vaccinated in Europe.

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

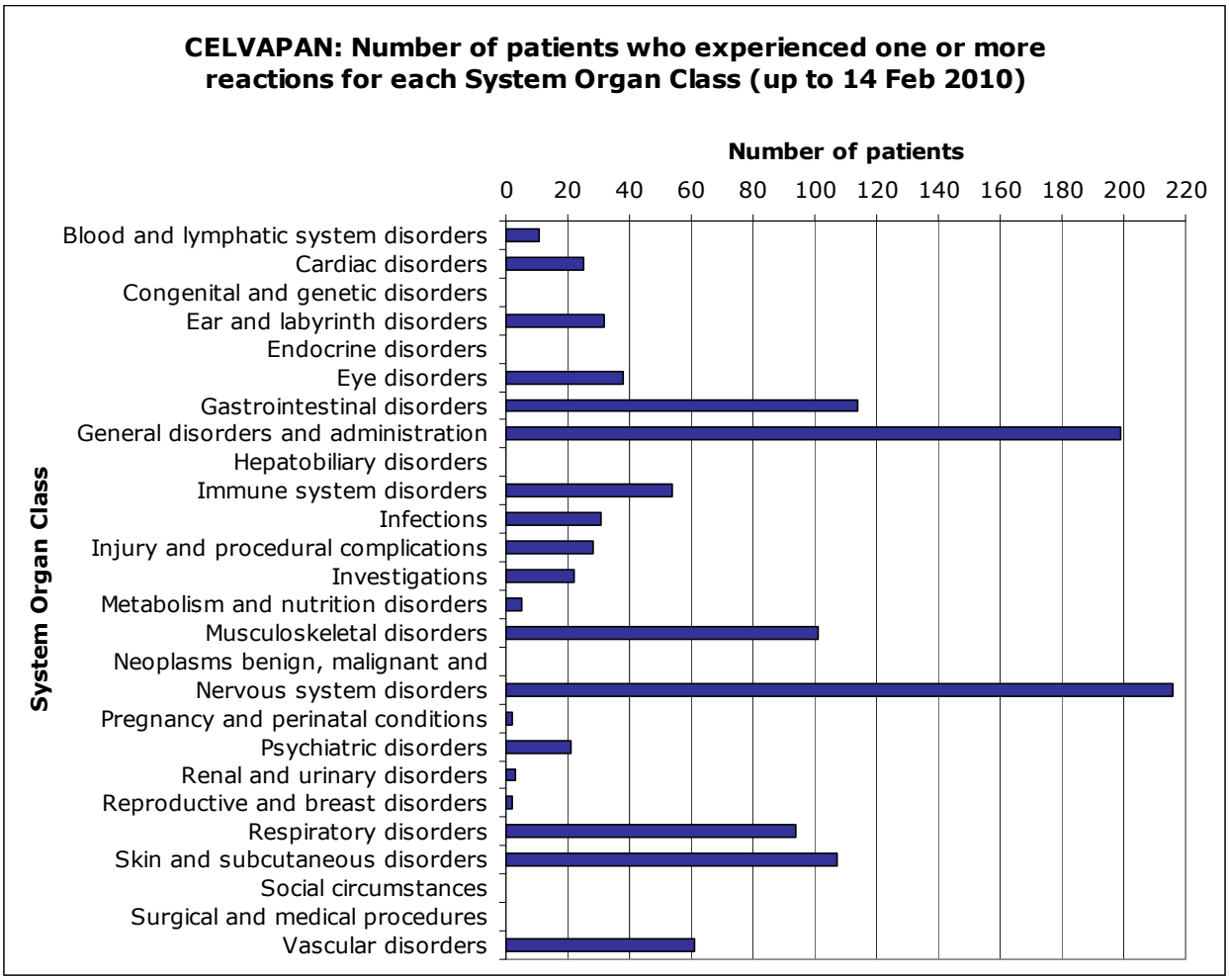
Arepanrix

Although authorised, Arepanrix is not marketed in the EEA but is available in Canada since October 2009. As of 14 February 2010, a total of 86 reports had been received by EudraVigilance from outside the EEA.

Following evaluation of the data presented in the periodic safety update report submitted by the company, it was concluded that the benefit-risk profile of the vaccine is favourable. No safety issue was identified.

Celvapan

As of 14 February 2010, a total of 471 reports had been received by EudraVigilance (an increase of 14 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 588,000 patients have been vaccinated with Celvapan in the EEA.



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

Distribution of adverse reactions by system organ class

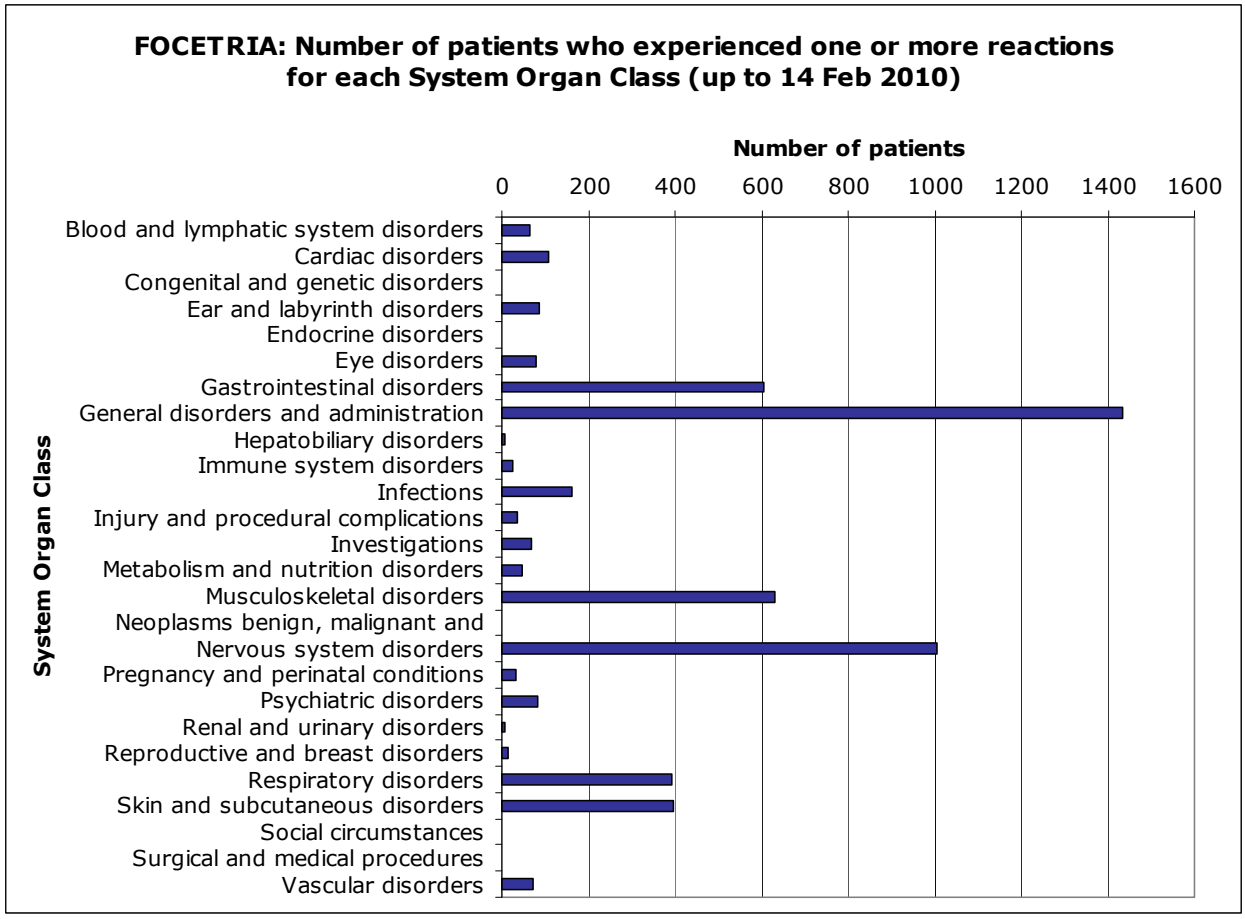
- In reports received from the EEA, the most frequently reported suspected adverse reactions in each system organ class (SOC) experienced by patients since the authorisation of the vaccine were:
  - Nervous-system disorders: headache, dizziness, syncope, paraesthesia, hypoaesthesia, lethargy;
  - General disorders and administration-site conditions: pyrexia, malaise, fatigue, chills, 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;
  - 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, nasopharyngitis;
  - Cardiac disorders: tachycardia, palpitations;
  - 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, medication error, pyrexia, dizziness, pallor, rash, headache, nausea, malaise, vision blurred, cough, chills, dyspnoea, fatigue, hyperhidrosis, pruritus and urticaria.
- Since the last update, no fatal cases have been reported in people vaccinated with Celvapan.
- The evaluation of the data presented in the third periodic safety update report submitted by the company concluded that the benefit-risk profile of the vaccine remains favourable. No new safety issue was identified. Additional data concerning cases of anaphylaxis have been requested to the company.
- The post-marketing section of the Summary of Product Characteristics has been amended with the addition of the following adverse reactions: febrile convulsion, pain in extremity (in the majority of cases reported as pain at the site of injection) and influenza-like illness.

Focetria

As of 14 February 2010, a total of 2,882 reports had been received by EudraVigilance (an increase of 11 reports since the previous update). Data available on 22 February 2010 from Member States and from the company[2] indicated that at least 36 million doses of Focetria had been distributed in the EEA, and at least 6.5 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, pain, injection-site pruritus, 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 25 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, rash generalised, swelling face, eczema;
- Respiratory disorders: cough, dyspnoea, oropharyngeal pain, asthma, bronchospasm, dysphonia, productive cough, throat irritation;
- Infections: rhinitis, nasopharyngitis, pneumonia, influenza, herpes zoster, pharyngitis;
- 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, anaphylactic reaction.

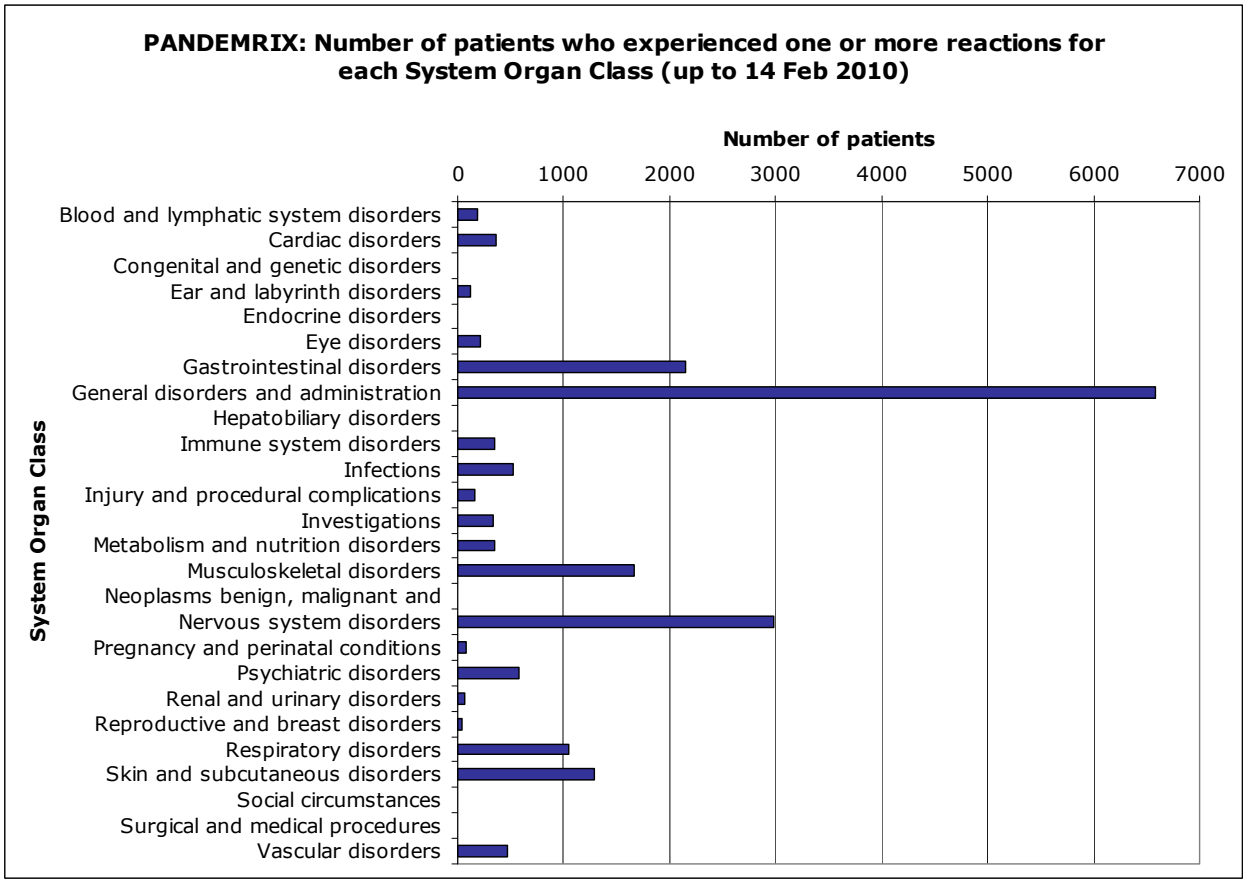
Updated safety information

- 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, urticaria, convulsion, and pain in extremity.
- Since the last update, no fatal cases have been reported in people vaccinated with Focetria.
- The post-marketing section of the Summary of Product Characteristics has been amended with the addition of the following terms: lymphadenopathy, palpitation, tachycardia, asthenia, muscular weakness, pain in extremities, cough and abdominal pain.
- Additional data from clinical trials carried-out in children have also been included:
  - Data in children and adolescents aged from three to 17 years suggest a slight decrease in reactogenicity after the second dose, with no increase in rates of fever. Very common reactions reported included pain, induration and erythema, malaise, myalgia, headache and fatigue.
  - Very common reactions reported in children between 12 and 35 months of age included tenderness, induration and erythema, irritability, unusual crying, sleepiness, diarrhoea and change in eating habits. Fever (≥38°C) has been reported in 14% of subjects aged from 12 to 35 months.
- Based on the evaluation of the data presented in the fourth periodic safety update report submitted by the company, it was concluded that the benefit-risk profile of the vaccine remains favourable. Nine cases of aggravation of pre-existing rheumatoid arthritis were identified. Additional data concerning the effects of influenza vaccinations in patients suffering from

autoimmune disease have been requested from the company. Additional information has also been requested regarding cases of anaphylaxis, Guillain-Barré syndrome, Bell's palsy, pneumonia and peripheral neuropathies.

Pandemrix

As of 14 February 2010, a total of 10,022 reports had been received by EudraVigilance (an increase of 203 reports since the previous update). Data available on 22 February 2009 from Member States and from the company[3] indicate that at least 85.6 million doses of Pandemrix had been distributed in the EEA. It is estimated that at least 28 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 erythema, injection-site swelling, pain, oedema peripheral, asthenia, injection-site induration, injection-site inflammation, chest pain, feeling hot, local reaction, chest discomfort;
  - Nervous-system disorders: headache, dizziness, paraesthesia, syncope, somnolence, hypoaesthesia, crying, febrile convulsion, convulsion, lethargy, tremor, loss of consciousness, presyncope, poor quality sleep, facial palsy, Guillain-Barré syndrome, hypersomnia, hypotonia;

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

- Gastrointestinal disorders: vomiting, nausea, diarrhoea, abdominal pain, upper abdominal pain, paraesthesia oral, lip swelling, dry mouth, swollen tongue, abdominal discomfort, hypoaesthesia oral, dysphagia, lower abdominal pain;
- 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, cold sweat, swelling face, rash erythematous, dermatitis allergic, rash macular, rash pruritic, pruritus generalised, facial hypoaesthesia, rash maculo-papular, eczema, petechiae, skin reaction, vesicular rash;
- Respiratory disorders: dyspnoea, cough, oropharyngeal pain, asthma, rhinorrhoea, wheezing, epistaxis, tachypnoea, throat tightness, pharyngeal oedema, sneezing, bronchospasm, respiratory failure, dysphonia, productive cough, pulmonary embolism, respiratory distress, hyperventilation, stridor;
- Psychiatric disorders: listlessness, insomnia, tearfulness, sleep disorder, restlessness, nightmare, hallucination, confusional state;
- Infections: rhinitis, nasopharyngitis, pneumonia, influenza, herpes zoster, swine influenza, cellulitis, bronchitis, ear infection, lower 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, body temperature decreased, heart rate decreased;
- Eye disorders: eye swelling, vision blurred, eye pain, ocular hyperaemia, eyelid oedema, diplopia, conjunctivitis;
- Blood and lymphatic system disorders: lymphadenopathy, thrombocytopenia;
- Injury and procedural disorders: medication error, vaccination failure, contusion;
- Ear and labyrinth disorders: vertigo, tinnitus, ear pain.

Updated safety information

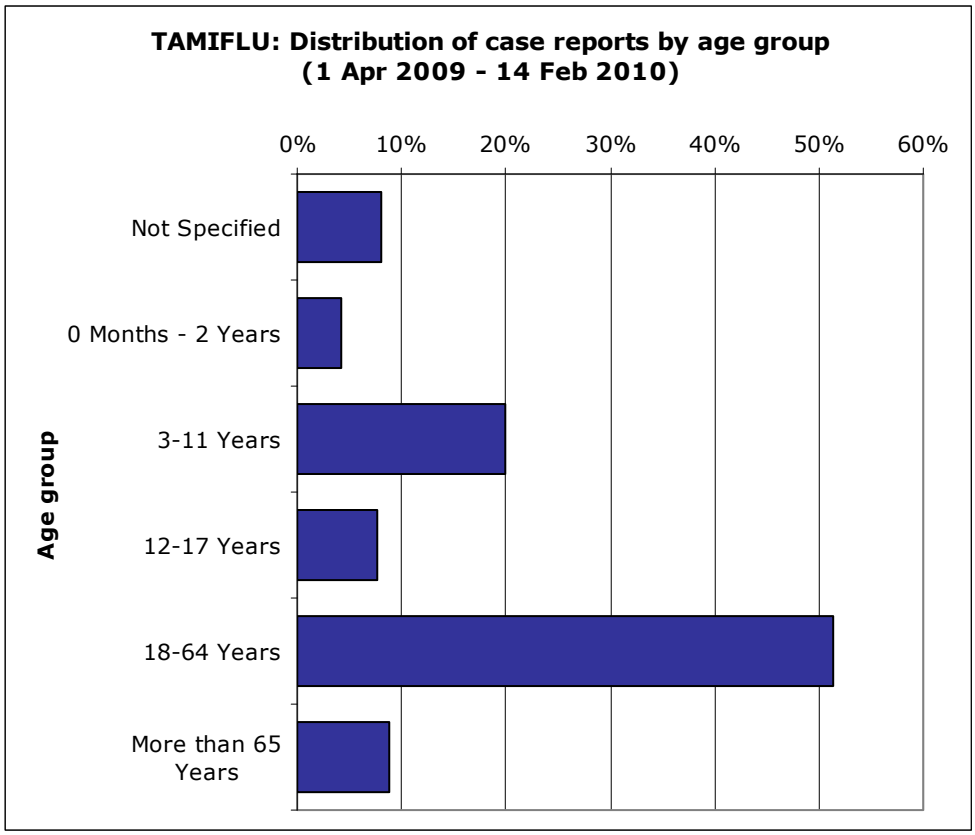
- Since the last update, six new fatal cases from the EEA have been received by EudraVigilance. They include four patients with cerebral haemorrhage or cardiovascular impairment. Three of these had a medical history of cardiovascular diseases. The two other deaths concerned a patient with an acute exacerbation of a chronic lung disease and a patient with a subarachnoid haemorrhage. There is no indication that the vaccine could have contributed to any of these fatal outcomes.
- The most frequently reported suspected adverse reactions in children since authorisation were pyrexia, hyperpyrexia, vomiting, injection-site pain, headache, diarrhoea, cough, fatigue, rash,

decreased appetite, nausea, abdominal pain, malaise, injection-site erythema, somnolence, listlessness, crying, injection site swelling, pallor, dyspnoea, syncope, influenza-like illness, myalgia, pain in extremity, febrile convulsion, urticaria and tearfulness.

Antiviral medicines

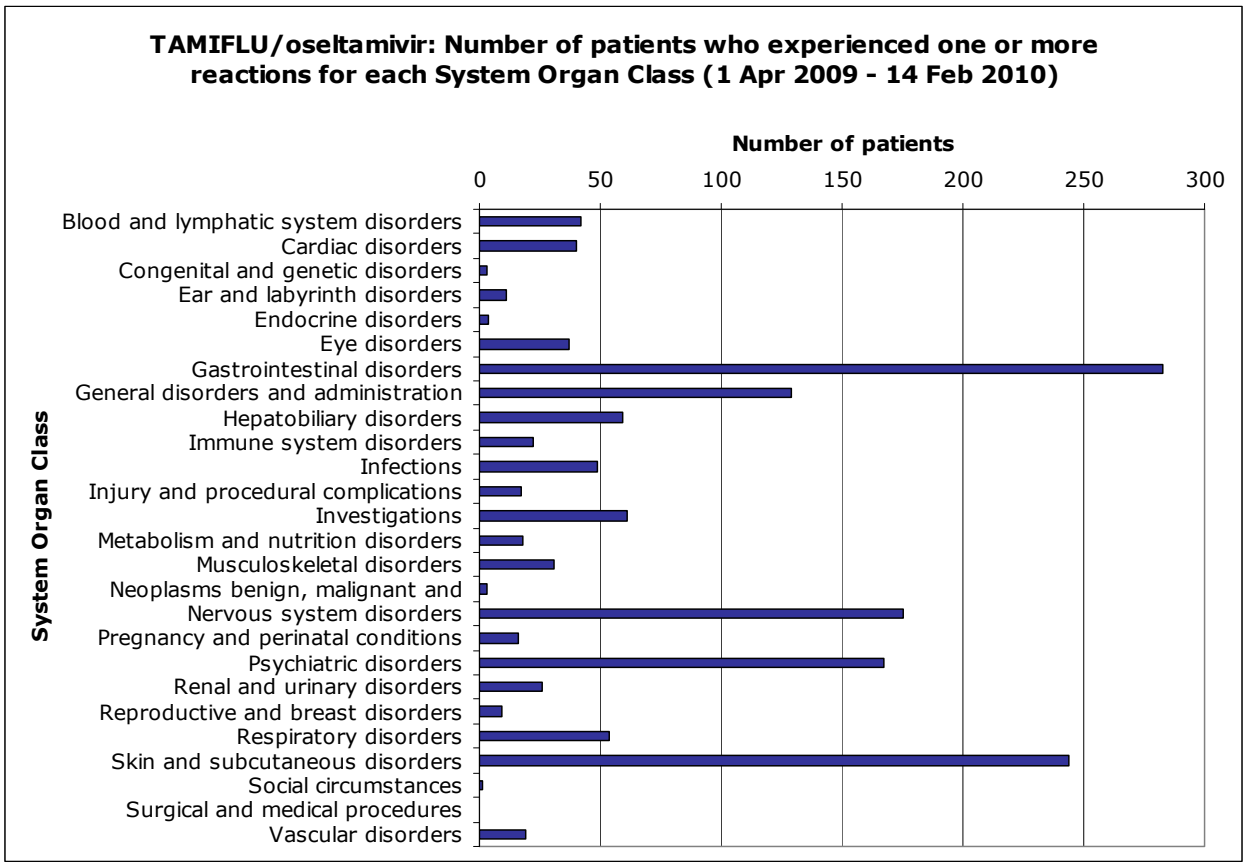
Tamiflu (oseltamivir)

From 1 April to 14 February 2010, a total of 1,015 reports worldwide were received by EudraVigilance (an increase of 13 reports since the previous update). The graph below displays the age distribution of patients who experienced an adverse reaction reported to EudraVigilance.



According to information received from the marketing authorisation holder, exposure to Tamiflu is estimated to be at least 21.1 million patients during the pandemic period of 1 May to 31 December 2009[4].

[4] As stated by the marketing authorisation holder in the pandemic safety report dated 27 January 2010.



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, lip swelling, mouth ulceration, pancreatitis, swollen tongue, dyspepsia, haematemesis, abdominal distension;
  - Skin and subcutaneous conditions: rash, urticaria, rash generalised, swelling face, erythema, pruritus, rash erythematous, rash pruritic, Stevens-Johnson syndrome, angioedema, dermatitis bullous, blister, erythema multiforme, rash macular, rash maculo-papular;
  - Nervous-system disorders: headache, convulsion, paraesthesia, dizziness, tremor, somnolence, epilepsy, syncope, burning sensation, cerebrovascular accident, nystagmus, dysgeusia;
  - Psychiatric disorders: hallucination, confusional state, nightmare, insomnia, anxiety, delirium, hallucination visual, disorientation, abnormal behaviour, agitation, panic attack, aggression, sleep disorder, depressed mood, mental disorder, psychotic disorder;
  - General disorders and administration-site conditions: malaise, death, pyrexia, chest pain, influenza-like illness, oedema peripheral, condition aggravated, drug interaction, fatigue, drug ineffective, general physical health deterioration, pain, face oedema, multi-organ failure, gait disturbance;

- Investigations: liver function test abnormal, hepatic enzyme increased, international normalised ratio increased, alanine aminotransferase increased, blood creatinine increased, gamma-glutamyltransferase increased, hepatic enzyme abnormal, prothrombin time prolonged;
- Respiratory disorders: epistaxis, dyspnoea, chronic obstructive pulmonary disease;
- Infections: pathogen resistance, influenza, pneumonia, bronchitis;
- Hepatobiliary disorders: hepatitis, cholestasis, hepatic failure, acute hepatic failure, cytolytic hepatitis.

Updated safety information

- Since the last update, one new worldwide report has been received by EudraVigilance with a fatal outcome following oseltamivir use. It concerned a patient who committed suicide at an unknown time after discontinuing oseltamivir treatment.
- 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, convulsion, nightmare, epistaxis, urticaria, headache, diarrhoea, nausea and abdominal pain.

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	Necrotising oesophagitis and necrotising stomatitis			6
	Pancreatitis	7		10
General disorders and administration site conditions	Death, sudden death	10	10	10
	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
Infections and infestations	Herpes zoster	9	9	9
Injury, poisoning and procedural complications	Medication error	7, 10		7, 10
Nervous system disorders	Acute disseminated encephalomyelitis (ADEM)		2, 3	
	Cerebral haemorrhage or infarction		1	3
	Demyelinating disorders	11	11	11
	Encephalitis		3, 5	
	Facial palsy or paresis	8	4, 8	7
	Guillain-Barré syndrome	4, 5, 11	2, 4, 5, 11	1, 3, 4, 5, 6, 11
	Multiple sclerosis	11	5, 11	5, 11
	Neuralgic amyotrophy			9
	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	11	2, 11	1, 2, 11

SOC	Topic	Update number		
		Celvapan	Focetria	Pandemrix
Skin and subcutaneous tissue disorders	Bullous dermatitis		9	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
Vascular disorders	Circulatory collapse	3		
	Vasculitis			6