10 March 2010
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Patient Health Protection

Thirteenth pandemic pharmacovigilance 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 28 February 2010. Except for Arepanrix, which is not marketed in the European Economic Area (EEA), the graphs represent aggregated data related to the 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 8 March 2010, at least 37.6 million people in the EEA, including at least 339,000 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 43.6 million people. Some of these have received two doses of a vaccine, but their percentage varies between countries.

The vast majority of the adverse reactions that had been reported as of 28 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.

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).

Pandemic information

In its weekly influenza surveillance overview dated 5 March 2010, the European Centre for Disease Prevention and Control (ECDC) concluded that the influenza activity caused by the 2009 pandemic influenza A(H1N1) virus is well past its winter peak in EU/EEA countries. The number of reported cases of serious acute respiratory infections and associated deaths continues to decline.

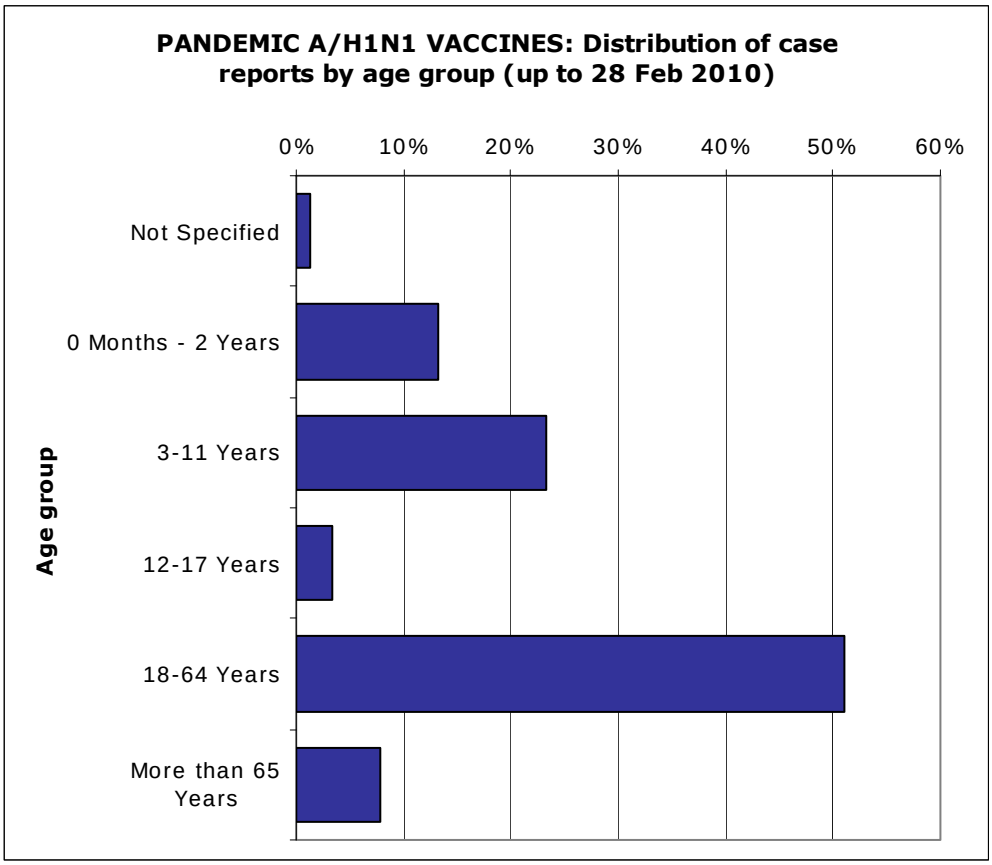
The number of confirmed fatal cases announced by EU/EEA Member States on their official websites as being due to the pandemic had reached 2,804 by 7 March 2010. The ECDC considers this figure to be an underestimation. Click here for the breakdown by country.

See the ECDC pandemic website, its current risk assessment and its weekly executive update for additional information. On March 8th, the ECDC issued a Forward Look Risk Assessment which attempts to identify the most likely scenario for influenza to the end of the 2010/2011 influenza season.

In its weekly update dated 5 March 2010, the World Health Organization stated that, as of 28 February 2010, worldwide more than 213 countries and overseas territories or communities have reported laboratory confirmed cases of pandemic influenza H1N1 2009, including at least 16,455 deaths. Transmission of virus persists in some areas of Europe and Asia but influenza activity is declining and is at a low level in most areas. The most active areas of transmission are currently observed in parts of Southeast Asia and Eastern and South-Eastern Europe.

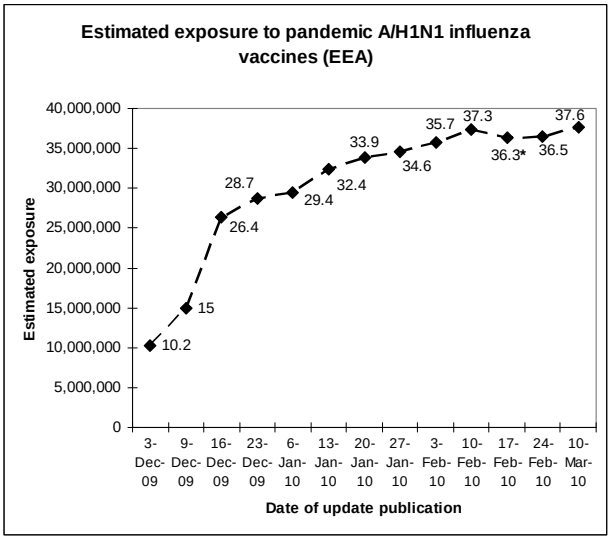
Overview of centrally authorised vaccines

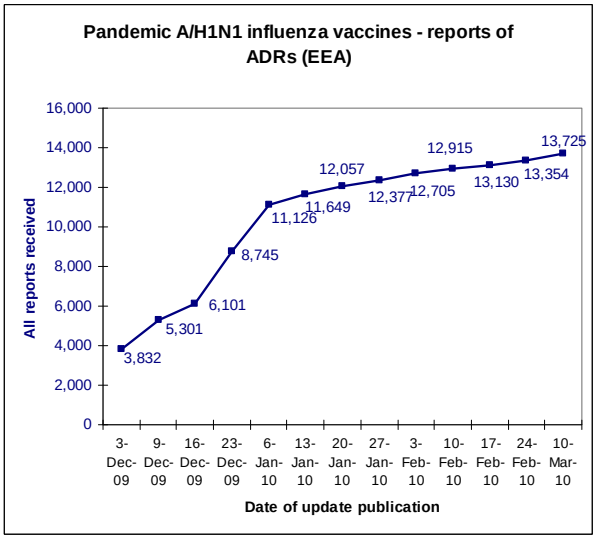
As of 28 February 2010, a total of 13,725 case reports had been received from the EEA by EudraVigilance since the authorisation of the three centrally authorised vaccines marketed in the EEA. This represents an increase of 371 reports compared with the previous update. The graph below displays the age distribution of all the reports received by EudraVigilance.



Data available on 8 March 2010 from Member States and from the vaccine marketing authorisation holders indicate that at least 145.9 million doses had been distributed and at least 37.6 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 339,000 pregnant women had been vaccinated. When the information available for the nationally authorised vaccines is included, at least 145.9 million doses had been distributed, with at least 43.6 million people (including at least 394,000 pregnant women) vaccinated in Europe.

The graphs below display the cumulative numbers of adverse reaction reports received by EudraVigilance for the three centrally-authorised vaccines marketed in the EEA 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 the number of new vaccinations with these three centrally-authorised vaccines.



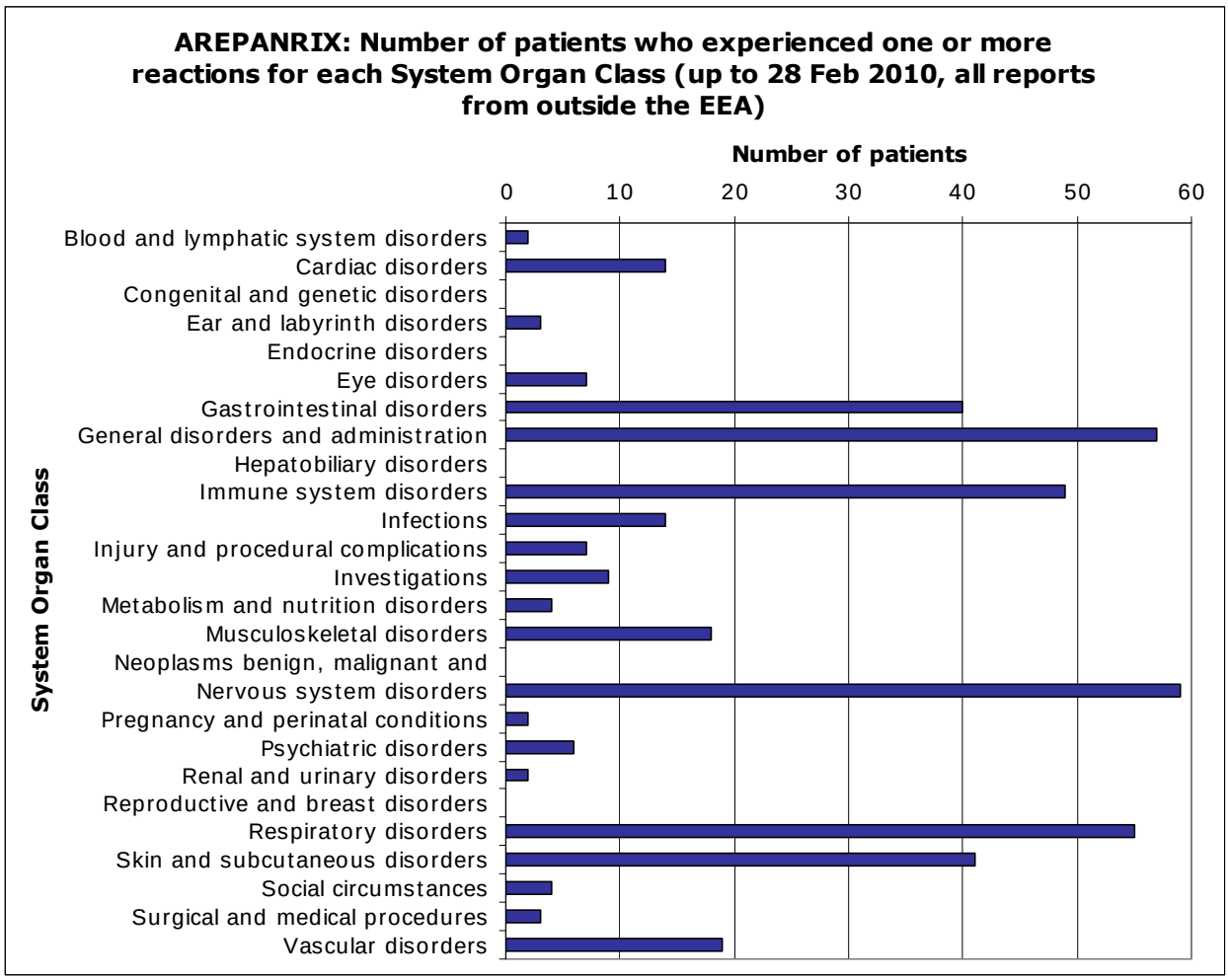


* This number decreased due to a correction in the number of vaccinated people in two Member States.

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 has been available in Canada since October 2009. In accordance with EU legislation, unexpected serious adverse reactions are reported from outside the EEA. As of 28 February 2010, a total of 106 reports had been received by EudraVigilance from outside the EEA. This represents an increase of 20 reports compared with the previous update.



Distribution of adverse reactions by system organ class

In reports of serious unexpected adverse reactions received from outside the EEA, the most frequently reported suspected adverse reactions in each system organ class (SOC) experienced by patients since the authorisation of the vaccine are listed below. Because known reactions to the vaccine are not reported from outside the EU, the profile of reports received for Arepanrix is different from those of the products marketed in the EU.

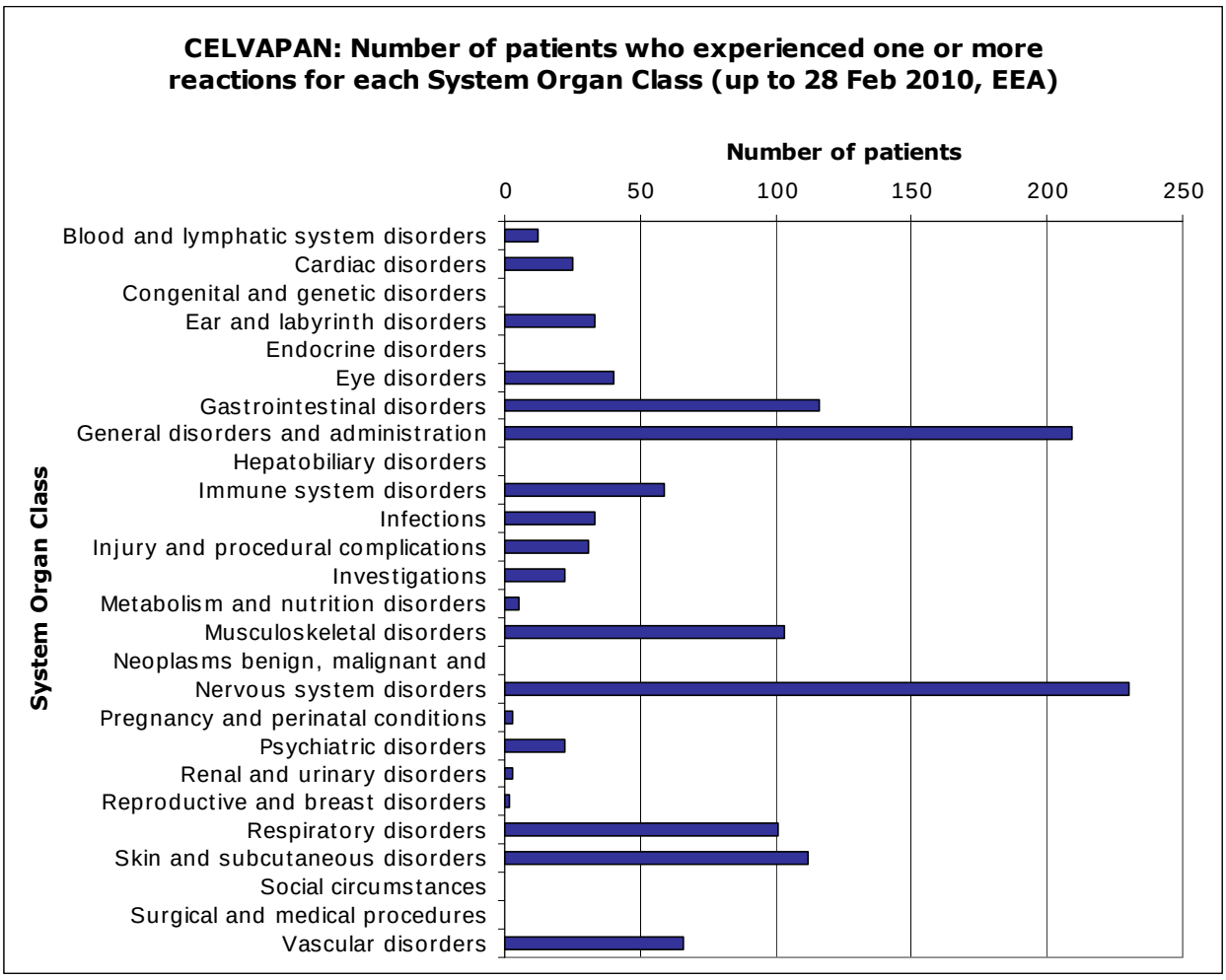
- Nervous-system disorders: Guillain-Barré syndrome, paraesthesia, dizziness, flaccid paralysis, hypoaesthesia;
- General disorders and administration-site conditions: product quality issue, asthenia, pyrexia, fatigue, chest discomfort;
- Respiratory disorders: dyspnoea, throat tightness, couch, pharyngeal oedema, respiratory paralysis;
- Immune disorders: anaphylactic reaction, hypersensitivity;
- Skin and subcutaneous conditions: angioedema, erythema, urticaria;
- Gastrointestinal disorders: nausea;
- Vascular disorders: flushing;
- Musculoskeletal disorders: muscular weakness;

– Cardiac disorders: cyanosis, tachycardia;

The most frequently reported suspected adverse reactions in children since authorisation included: dyspnoea, urticaria, anaphylactic reaction, angioedema, cough, and erythema.

Celvapan

As of 28 February 2010, a total of 501 reports had been received by EudraVigilance (an increase of 30 reports since the previous update). According to the information provided by the company[1] and Member States, at least 9.1 million doses had been distributed to EEA countries up to 8 March 2010. It is estimated that at least 659,000 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, somnolence;

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

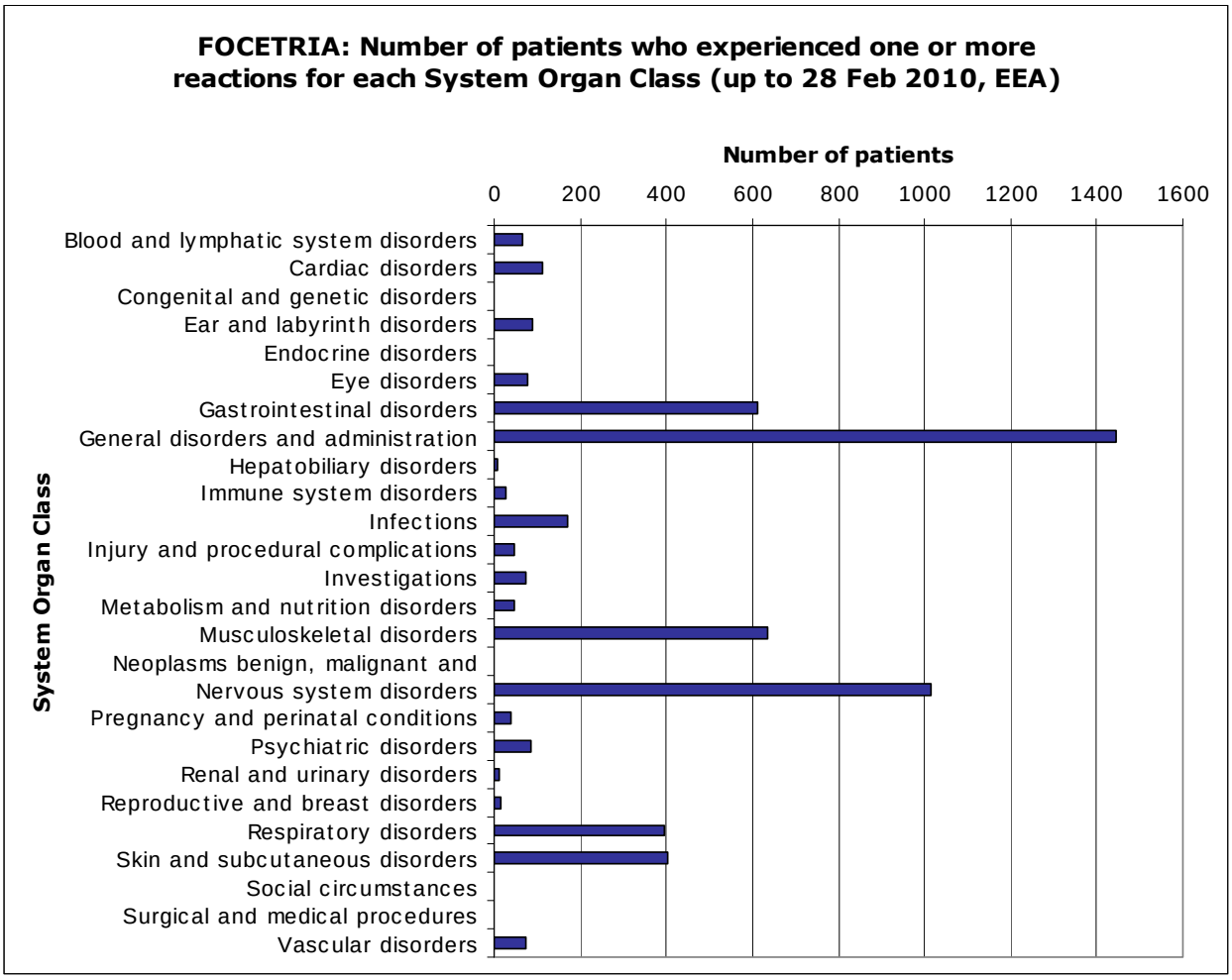
- General disorders and administration-site conditions: pyrexia, malaise, fatigue, chills, asthenia, influenza-like illness, feeling hot, injection-site pain, chest discomfort, pain;
- Gastrointestinal disorders: nausea, vomiting, diarrhoea, abdominal pain, oral paraesthesia;
- Skin and subcutaneous conditions: hyperhidrosis, pruritus, rash, urticaria, rash, erythema;
- Musculoskeletal disorders: myalgia, arthralgia, pain in extremity, muscular weakness, muscle spasms;
- Respiratory disorders: cough, oropharyngeal pain, dyspnoea, asthma, rhinorrhoea, wheezing;
- Vascular disorders: pallor, flushing, hypotension;
- Immune disorders: hypersensitivity, anaphylactic reaction, anaphylactoid reaction;
- Eye disorders: vision blurred;
- Infections: rhinitis, nasopharyngitis;
- Ear and labyrinth disorders: vertigo;
- Injury and procedural complications: medication error;
- Cardiac disorders: tachycardia, palpitations;
- Psychiatric disorders: sleep disorders;
- Investigations: body temperature increased.

Updated safety information

- The most frequently reported suspected adverse reactions in children since authorisation included hypersensitivity, vomiting, medication error, syncope, 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.

Focetria

As of 28 February 2010, a total of 2,921 reports had been received by EudraVigilance (an increase of 39 reports since the previous update). Data available on 8 March 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, pain, asthenia, 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;

[2] As stated by the marketing authorisation holder in the periodic safety update report dated 25 January 2010.

- Musculoskeletal disorders: myalgia, pain in extremity, arthralgia, musculoskeletal stiffness, muscular weakness, neck pain, muscle spasms, musculoskeletal pain, back pain, sensation of heaviness, rheumatoid arthritis, arthritis;
- 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, laryngeal oedema;
- 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: listless, 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.

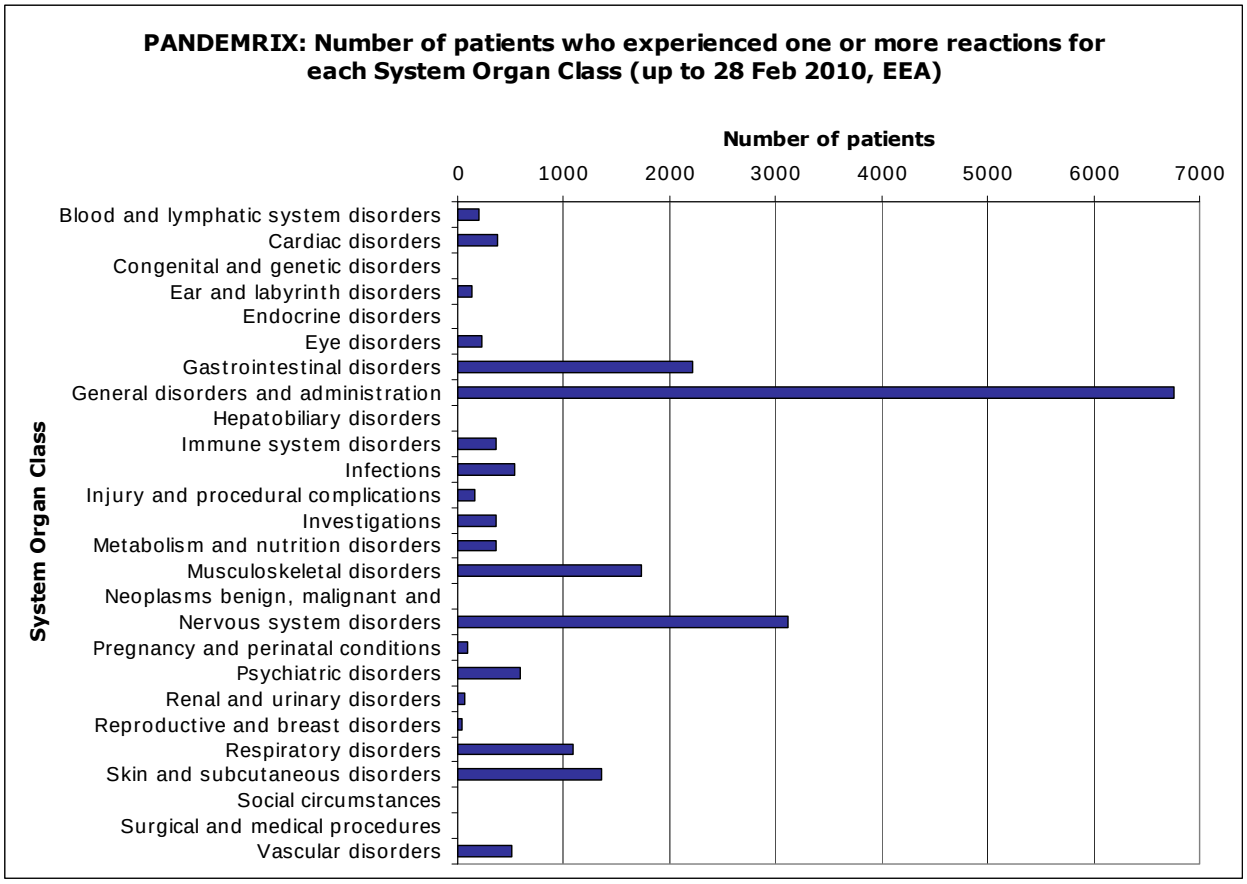
Updated safety information

- 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, asthma and decreased appetite.
- Since the last update, no fatal cases have been reported in people vaccinated with Focetria.
- In the eighth update, it was mentioned that, since authorisation, ten reports mentioning ‘seizure’ as an adverse reaction had been received by EudraVigilance. As many factors can precipitate epileptic fits, the small number of reported cases was not suggestive of a causal association with the vaccine. This issue has been closely monitored and further information and analyses have been requested from the company. After an evaluation of this information, it was concluded that there was no evidence that Focetria could increase the risk of seizures or convulsions.

Pandemrix

As of 28 February 2010, a total of 10,326 reports had been received by EudraVigilance (an increase of 304 reports since the previous update). Data available on 8 March 2010 from Member States and from

the company[3] indicate that at least 100.7 million doses of Pandemrix had been distributed in the EEA. It is estimated that at least 30.4 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, local reaction;
  - Nervous-system disorders: headache, dizziness, paraesthesia, syncope, somnolence, crying, hypoaesthesia, febrile convulsion, convulsion, lethargy, tremor, loss of consciousness, presyncope, Guillain-Barré syndrome, hypersomnia, poor quality sleep, facial palsy, hypotonia;
  - Gastrointestinal disorders: vomiting, nausea, diarrhoea, abdominal pain, upper abdominal pain, paraesthesia oral, lip swelling, swollen tongue, dry mouth, abdominal discomfort, hypoaesthesia oral, dysphagia, lower abdominal pain;
  - Musculoskeletal disorders: myalgia, pain in extremity, arthralgia, musculoskeletal stiffness, muscular weakness, back pain, musculoskeletal pain, limb discomfort, neck pain, muscle spasms, arthritis;

[3] As stated by the marketing authorisation holder in the periodic safety update report dated 12 February 2010.

- Skin and subcutaneous conditions: rash, urticaria, erythema, hyperhidrosis, pruritus, rash generalised, angioedema, cold sweat, swelling face, rash erythematous, rash macular, dermatitis allergic, rash pruritic, pruritus generalised, facial hypoaesthesia, rash maculo-papular, petechiae, eczema, vesicular rash, skin reaction,;
- Respiratory disorders: dyspnoea, cough, oropharyngeal pain, asthma, rhinorrhoea, wheezing, epistaxis, tachypnoea, throat tightness, bronchospasm, pharyngeal oedema, sneezing, respiratory failure, dysphonia, respiratory distress, productive cough, pulmonary embolism, hyperventilation, stridor;
- Psychiatric disorders: listlessness, insomnia, tearfulness, sleep disorder, restlessness, hallucination, nightmare, confusional state;
- Infections: rhinitis, pneumonia, nasopharyngitis, influenza, herpes zoster, swine influenza, cellulitis, bronchitis, lower respiratory tract infection, ear infection, respiratory tract infection;
- Vascular disorders: pallor, circulatory collapse, hypotension, flushing, hypertension, peripheral coldness, hot flush, hypertensive crisis;
- Cardiac disorders: tachycardia, palpitations, cyanosis, myocardial infarction, cardiac failure, atrial fibrillation, cardiac arrest, angina pectoris, bradycardia;
- Immune disorders: hypersensitivity, anaphylactic reaction, anaphylactic shock, anaphylactoid reaction;
- Metabolism and nutrition disorders: decreased appetite, oligodipsia, dehydration, polydipsia;
- Investigations: body temperature increased, blood pressure decreased, blood pressure increased, heart rate increased, heart rate decreased, body temperature decreased;
- Eye disorders: eye swelling, vision blurred, eye pain, eye swelling, ocular hyperaemia, eyelid oedema, diplopia, conjunctivitis, photophobia;
- 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

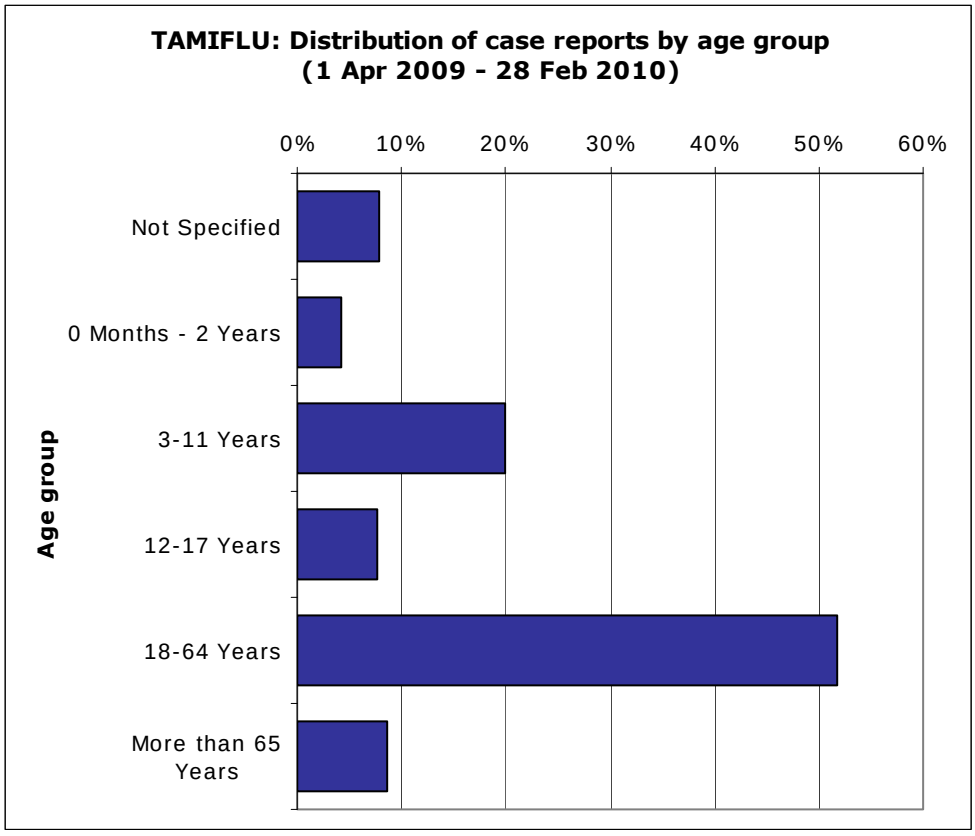
- Since the last update, six new fatal cases from the EEA have been received by EudraVigilance. They concerned four men and two women with ages ranging from 61 to 81 years. Three of the fatal cases resulted from respiratory arrest, one resulted from sudden cardiac death, one resulted from cardiac arrest and one resulted from acute myocardial infarction, ventricular fibrillation and cardiac arrest. There was no suggestion that Pandemrix could have contributed to these deaths.
- The most frequently reported suspected adverse reactions in children since authorisation were pyrexia, hyperpyrexia, vomiting, injection-site pain, headache, diarrhoea, cough, rash, fatigue, decreased appetite, nausea, abdominal pain, malaise, injection-site erythema, crying, somnolence, listlessness, injection site swelling, pallor, syncope, dyspnoea, influenza-like illness, pain in extremity, myalgia, febrile convulsion, urticaria and tearfulness.
- In the fourth update there were three reported cases of seizures with a fatal outcome in known epileptic patients, which occurred in temporal association with Pandemrix vaccination. A search for additional cases across Europe had revealed a further 34 cases of seizures occurring in known

epileptic patients following vaccination with Pandemrix. Given that a very large number of persons have received Pandemrix, no conclusion about a causal relationship with vaccine could be drawn, but it was announced this issue would be further investigated. Analysis of the available data did not raise any specific concern. In order to collect additional data, an epidemiological study will be carried out and will compare the occurrence of seizures in epileptic patients who have been vaccinated with Pandemrix with the occurrence in epileptic patients who did not receive the vaccine.

Antiviral medicines

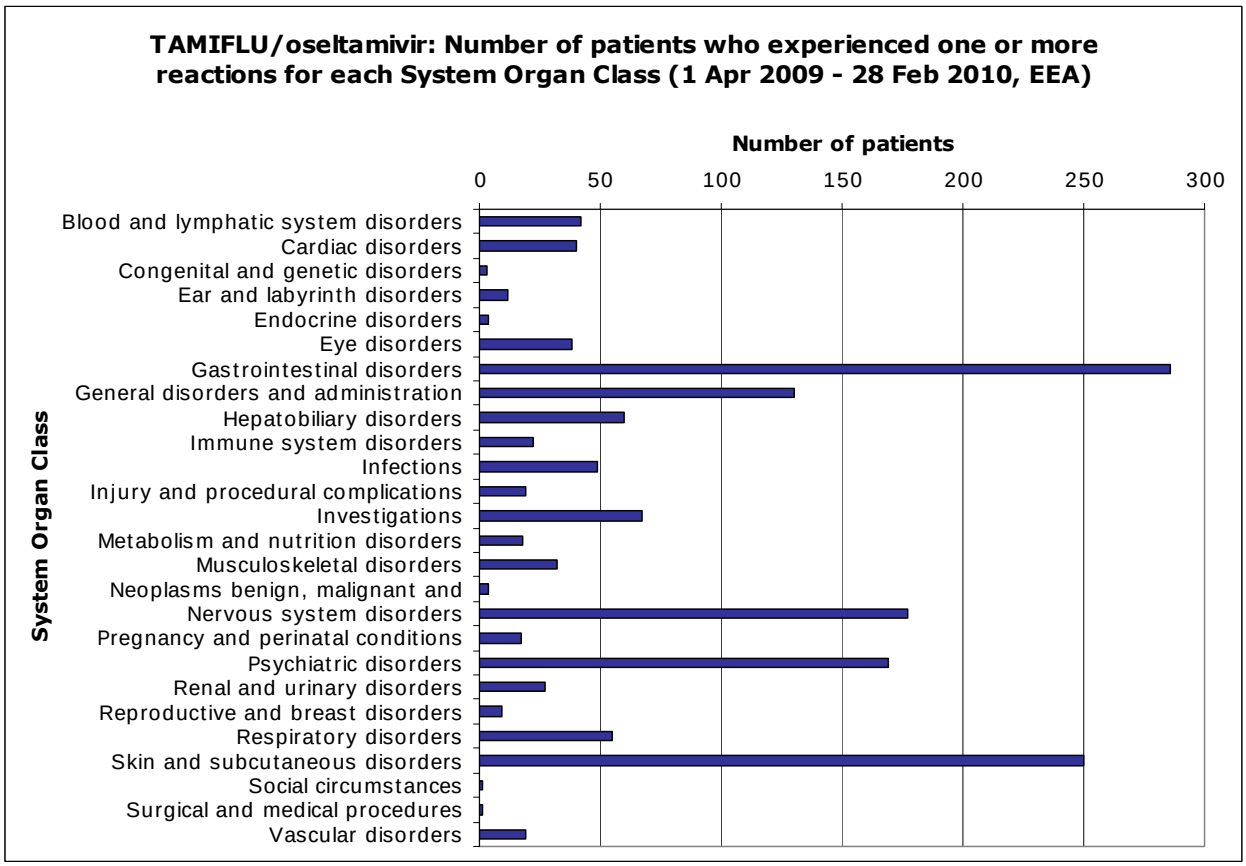
Tamiflu (oseltamivir)

From 1 April to 28 February 2010, a total of 1,033 reports worldwide were received by EudraVigilance (an increase of 18 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, haemorrhagic diarrhoea, gastrointestinal haemorrhage;
  - Skin and subcutaneous conditions: rash, urticaria, rash generalised, erythema, swelling face, pruritus, Stevens-Johnson syndrome, rash erythematous, rash pruritic, 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, coordination abnormal, dysgeusia, psychomotor hyperactivity;
  - 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, gait disturbance, multi-organ failure;

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

Updated safety information

- Since the last update, nine new worldwide reports have been received by EudraVigilance with a fatal outcome following oseltamivir use. They concerned five deaths following pneumonia, influenza or acute respiratory infection, one death due to stroke, one death due to meningitis, one death due to a multiorgan failure associated with infection and one death due to respiratory failure in a patient recently diagnosed with congestive heart failure associated with an acute myocardial infarction. There is no indication that oseltamivir contributed to any of these deaths.
- 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