EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Patient Health Protection

Eighth 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 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 by EudraVigilance up to 17 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 25 January 2010, in the EEA, at least 34.6 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 38.6 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 17 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.

On 22 January 2010, the European Medicines Agency published a press release announcing that the Agency's Committee for Medicinal Products for Human Use (CHMP) had recommended the granting of a conditional marketing authorisation for a fourth pandemic vaccine, Arepanrix. Further clinical studies of this vaccine are ongoing in children, adolescents and adults and results will become available from March 2010. Information on Arepanrix will be included in these weekly updates when it has received a marketing authorisation from the European Commission.

In this update, an analysis is presented of 825 adverse reaction reports received in EudraVigilance up to 17 January 2010 that did not mention the brand name of the pandemic vaccine. These were reported as being linked to a 'pandemic vaccine' or similar. The adverse reactions included in these reports are consistent with the safety profiles described in the product information for the vaccines authorised in the European Union (EU). The European Medicines Agency encourages the marketing authorisation holders and national competent authorities to take all necessary steps to contact the primary sources of these reports so that further information can be obtained to enable the identification of the vaccines administered.

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 antiviral (Tamiflu), visit the Agency's pandemic influenza (H1N1) website.

For information on 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 22 January 2010, the European Centre for Disease Prevention and Control (ECDC) stated that during the second week of 2010 only Bulgaria, Malta, Poland and Romania reported medium influenza-like illness (ILI) or acute respiratory infection (ARI) activity in the European Economic Area (EEA). During that week, of 684 sentinel samples tested, 18.1% were positive for influenza, of which more than 99% were 2009 pandemic influenza A(H1N1) virus. The number of cases of serious acute respiratory infection (SARI), measured by week of onset, continued to decline in the second week of 2010. Of the 123 SARI cases, 44 (36%) were known to have required admission to an intensive care unit and 28 (23%) needed respiratory support. The detection of 2009 pandemic influenza A(H1N1) viruses resistant to oseltamivir remains sporadic only. Of 1,260 viruses reported, 34 (2.7%) were resistant.

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

In its weekly update dated 22 January 2010, the World Health Organization stated that, as of 17 January 2010, worldwide more than 209 countries and overseas territories or communities had reported laboratory-confirmed cases of pandemic influenza H1N1 2009, including at least 14,142 deaths. The overall situation was largely unchanged since the previous week. The most intense transmission of pandemic influenza virus continued to occur in North Africa, South Asia, and in limited areas of Eastern Europe. Overall pandemic influenza activity in the temperate northern hemisphere peaked between late October and late November 2009 and had continued to decline since.

Overview of centrally authorised vaccines

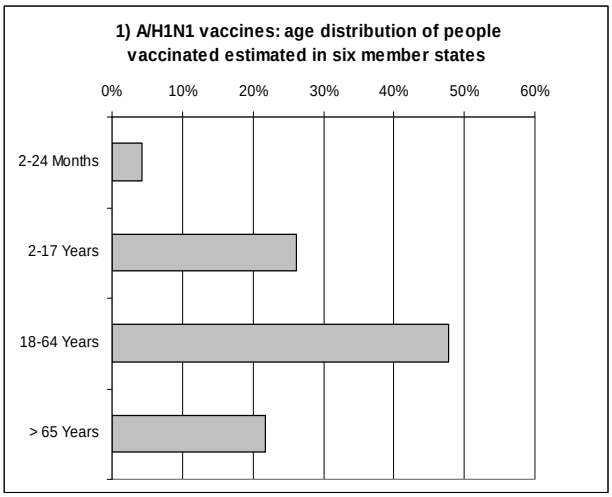
As of 17 January 2010, a total of 12,377 case reports had been received by EudraVigilance since the authorisation of the three centrally authorised vaccines. This represents an increase of 329 reports compared with the previous update, reflecting the increase in the number of people vaccinated.

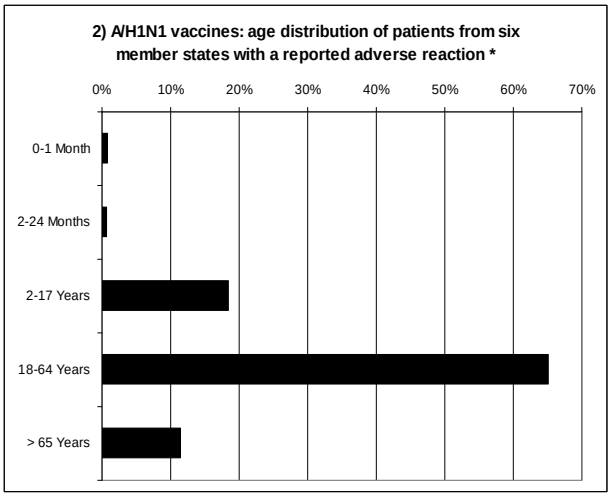
Data available on 25 January 2010 from Member States and from the vaccine's marketing-authorisation holders indicated that at least 125.8 million doses had been distributed and at least 34.6 million patients had been vaccinated with one of the three centrally authorised vaccines in the EEA. From the limited information received from seven EEA countries by 25 January 2010, at least 261,000. pregnant women had been vaccinated.

When the information available for the nationally authorised vaccines is included, at least 130.1 million doses have been distributed, with at least 38.6 million people (including at least 296,000 pregnant women) vaccinated in Europe.

The graphs below show:

1. the estimated age distribution of people vaccinated in the six EEA Member States for which sufficient information was available (Belgium, Denmark, France, Greece, Norway and Portugal);
2. the age distribution of patients from these countries who experienced an adverse reaction reported to EudraVigilance. A high percentage of adverse drug reaction reports in the 18-64-year category was observed in the six countries.



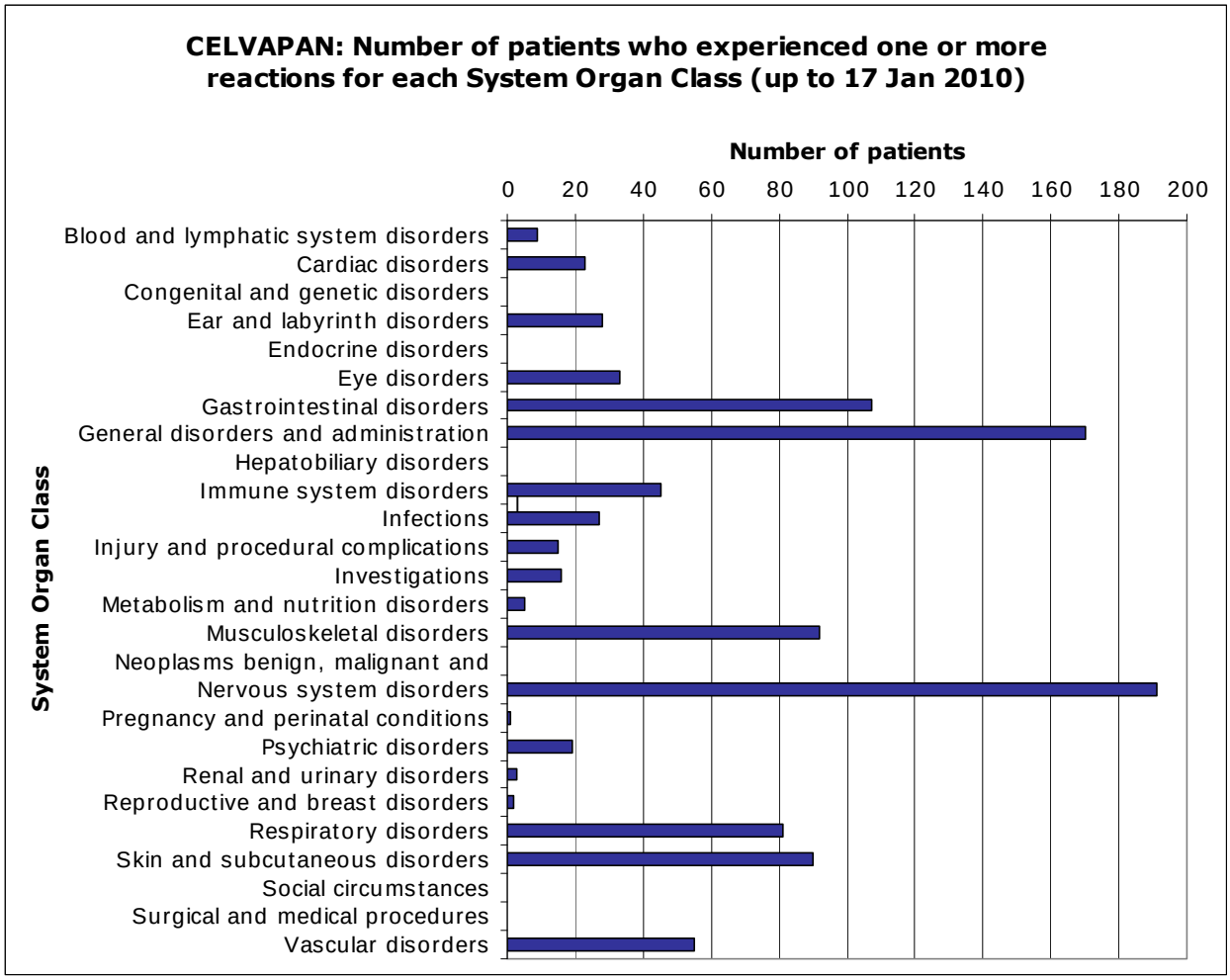


* Age was not specified in 3.4% of the reports.

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

Celvapan

As of 17 January 2010, a total of 401 reports had been received by EudraVigilance (an increase of eight since the previous update). According to the information provided by the company[1] and Member States, a total of 6,006,000 doses had been distributed to EEA countries up to 29 December 2009. It is estimated that at least 480,000 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 frequent 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;
  - General disorders and administration-site conditions: pyrexia, chills, malaise, fatigue, asthenia, influenza-like illness, feeling hot, chest discomfort, injection-site pain;
  - 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;

[1] As stated by the marketing-authorisation holder in the periodic safety update report dated 23 December 2009.

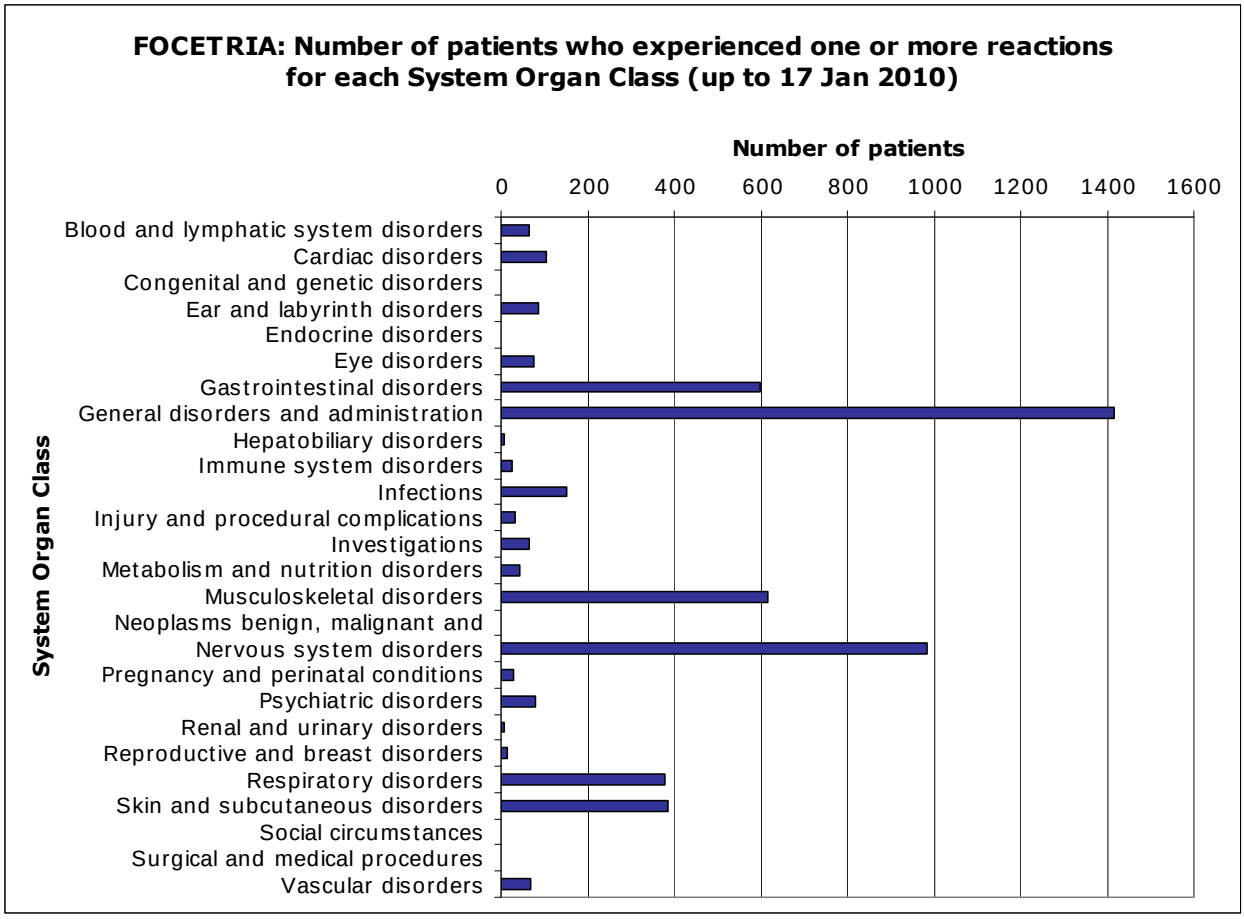
- Respiratory disorders: cough, oropharyngeal pain, dyspnoea;
- Vascular disorders: pallor, flushing, hypotension;
- Immune disorders: hypersensitivity, anaphylactic reaction, anaphylactoid reaction;
- Eye disorders: vision blurred;
- Ear and labyrinth disorders: vertigo;
- Infections: rhinitis;
- Cardiac disorders: tachycardia;
- Psychiatric disorders: sleep disorders.

Updated safety information

- The most frequently reported suspected adverse reactions in children since authorisation include hypersensitivity, vomiting, pyrexia, syncope, dizziness, pallor, nausea, headache, rash, cough, chills, hyperhidrosis, medication error and vision blurred.
- Since the last update, no fatal cases have been reported in people vaccinated with Celvapan.
- Since the last update, a report has been received concerning a 12-year old child who developed facial nerve paresis one week after the second dose of Celvapan. The child was hospitalised and additional investigations did not show any pathological alterations. He recovered about two weeks after the onset of the reaction. Reports of facial palsy are also discussed in relation to Focetria below.

Focetria

As of 17 January 2010, a total of 2,807 reports had been received by EudraVigilance (an increase of 52 reports since the previous update). Data available on 25 January 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 7.6 million patients had been vaccinated.



Distribution of adverse reactions by system organ class

- In reports received from the EEA, the most frequent 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, injection-site pruritus, pain, asthenia, feeling cold, injection-site haematoma, feeling hot, injection-site warmth;
  - Nervous-system disorders: headache, dizziness, paraesthesia, tremor, somnolence, dysgeusia, syncope, hypoaesthesia, presyncope, convulsion, 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, erythema, urticaria, 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;
- Eye disorders: eyelid oedema, visual impairment, eye irritation, eye swelling;
- Vascular disorders: hypotension, flushing, hypertension, pallor;
- Investigations: body temperature increased.

Updated safety information

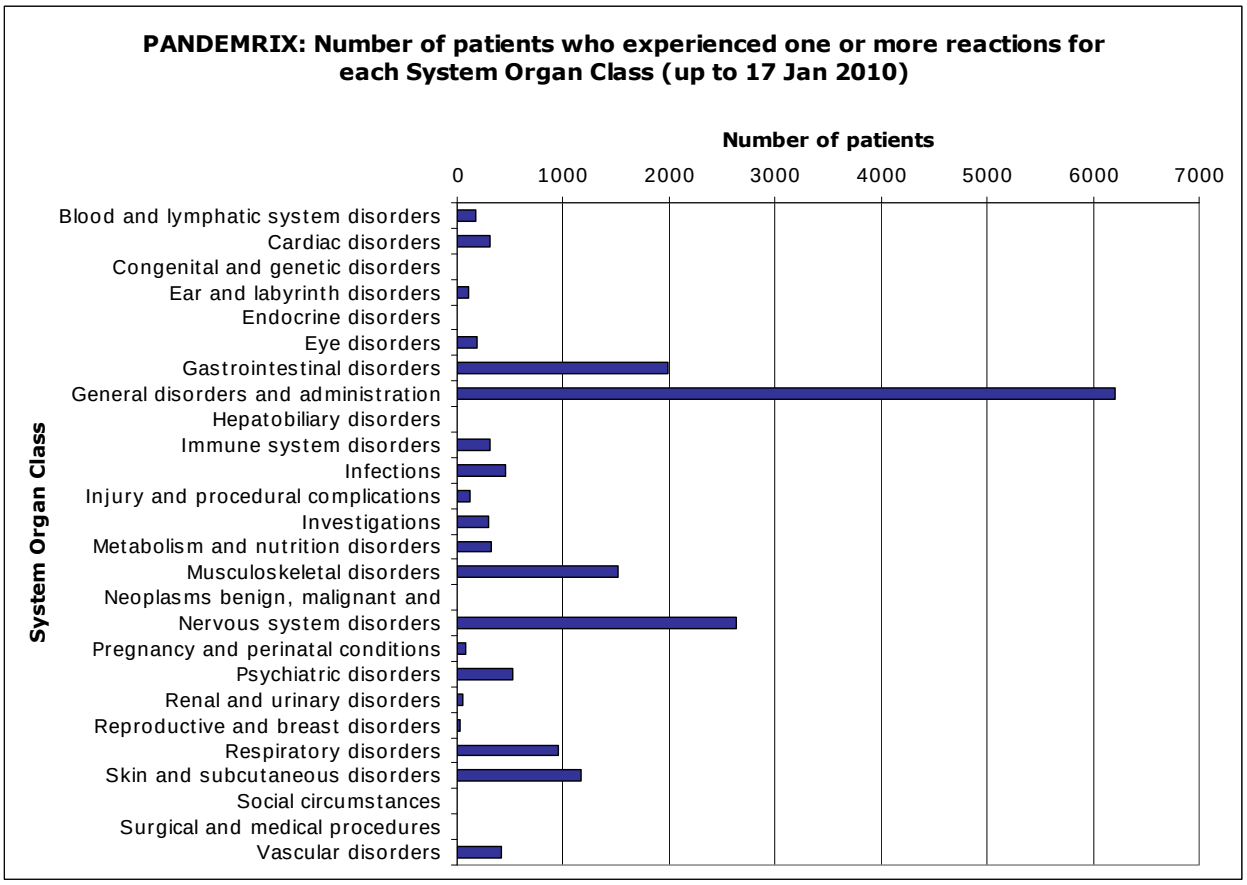
- The most frequently reported suspected adverse reactions in children since authorisation include pyrexia, headache, hyperpyrexia, vomiting, cough, nausea, abdominal pain, diarrhoea, injection-site pain, myalgia, fatigue, influenza-like illness, rash, dyspnoea, malaise, convulsion, pain in extremity and urticaria.
- Since the last update, no new fatal cases have been received in EudraVigilance.
- The third periodic safety update report has been submitted by the company. Following evaluation, it was concluded that the benefit-risk balance of Focetria remains positive. The company was asked to provide additional information on reported cases of arthritis, peripheral neuropathies, muscular weakness, pneumonia, unexplained deaths, Guillain-Barré syndrome, encephalomyelitis, neuritis, Bell's palsy and vasculitis. The company was also asked to provide further data on pregnant women who have been vaccinated.
- Since authorisation, seven cases of paralysis or paresis have been received by EudraVigilance. They include four cases of facial paresis (two of which occurred in pregnant women), which developed after delays of five to 16 days following the vaccination. Reports of facial palsy are discussed below. The three other cases reported as paralysis and paresis included one case of hemiplegia following cerebral ischaemia, a poorly documented case of leg paralysis in an 87-year-old woman, and a poorly documented case of left foot and hand weakness in a 55-year-old man with underlying medical conditions who had had the same symptoms in the past. These cases do not suggest a causal association with Focetria.
- Since authorisation, ten reports mentioning 'seizure' as an adverse reaction have been received by EudraVigilance. For two of these reports, the information provided was not sufficient to allow assessment. The eight other reports concerned one child and seven adults. Six patients had a history of epilepsy, three of whom presented with epileptic fits following both the first and the second doses of Focetria. In two of these cases, the latency ranged from two to four days, which is not indicative of a relationship with the vaccine. In the third case, the patient presented with an epileptic fit one hour after the first vaccination. In the other cases, concomitant events could have precipitated an epileptic fit, such as fever or headache. An 87-year-old woman who had presented

with convulsions three days after the vaccination died two days later of an unknown cause. As many factors can precipitate epileptic fits, the small number of reported cases does not suggest a causal association with the vaccine. This issue is being closely monitored. Further information and analyses have been requested from the company.

- A review of six cases of facial palsy reported in relation to Focetria was presented in the fourth update. Three additional cases have been received since the fourth update, with an unknown latency in one case and with times to onset of five days and two weeks in the other cases. These are not suggestive of a causal relationship with the vaccine. These three cases do not modify the conclusion of the fourth update: there are many possible causes for the occurrence of facial palsy, but in most cases the cause is unknown. Data from the United Kingdom reported the incidence of facial palsy as 12 per 100,000 people per year in patients below 17 years of age, and up to 45 per 100,000 people per year in older patients. Given the large number of patients vaccinated, there remains no evidence that the vaccine is associated with facial palsy.

Pandemrix

As of 17 January 2010, a total of 9,179 reports had been received by EudraVigilance (an increase of 270 reports since the previous update). Data available on 25 January 2009 from Member States and from the company[3] indicated that at least 82 million doses of Pandemrix had been distributed in the EEA. It is estimated that at least 24.5 million patients have been vaccinated.



Distribution of adverse reactions by system organ class

- In reports received from the EEA, the most frequent 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;
  - Nervous-system disorders: headache, dizziness, paraesthesia, somnolence, syncope, crying, hypoaesthesia, febrile convulsion, lethargy, convulsion, tremor, loss of consciousness, poor quality sleep, presyncope, hypersomnia;
  - Gastrointestinal disorders: vomiting, nausea, diarrhoea, abdominal pain, upper abdominal pain, paraesthesia oral, lip swelling, dry mouth, swollen tongue, hypoaesthesia oral, abdominal discomfort, lower abdominal pain, dysphagia;

[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, petechiae, pruritus generalised;
- Respiratory disorders: cough, dyspnoea, oropharyngeal pain, rhinorrhoea, asthma, wheezing, epistaxis, tachypnoea, pharyngeal oedema, throat tightness, bronchospasm, sneezing, dysphonia, respiratory failure;
- Psychiatric disorders: listlessness, insomnia, tearfulness, sleep disorder, restlessness, nightmare, confusional state;
- Infections: rhinitis, nasopharyngitis, pneumonia, influenza, herpes zoster, swine influenza, cellulitis;
- Vascular disorders: pallor, hypotension, circulatory collapse, flushing, hypertension, hot flush, peripheral coldness;
- Metabolism and nutrition disorders: decreased appetite, oligodipsia, dehydration;
- Investigations: body temperature increased, blood pressure decreased, blood pressure increased, heart rate increased;
- Immune disorders: hypersensitivity, anaphylactic reaction, anaphylactic shock, anaphylactoid reaction;
- Cardiac disorders: tachycardia, palpitations, cyanosis, myocardial infarction, cardiac failure, atrial fibrillation;
- Eye disorders: eye swelling, eye pain, vision blurred, ocular hyperaemia, eyelid oedema;
- Ear and labyrinth disorders: vertigo, ear pain, tinnitus.

Updated safety information

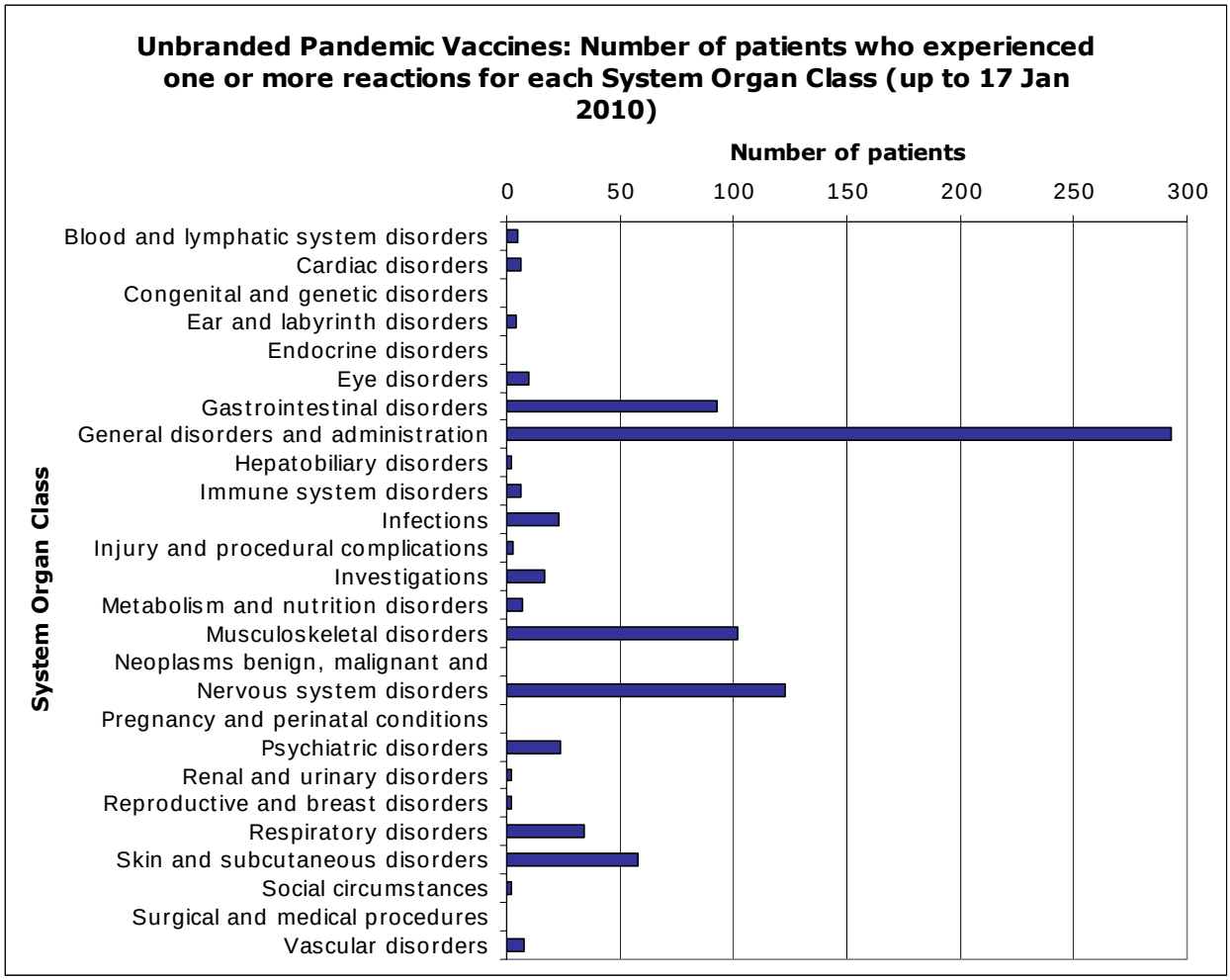
- Since the last update, seven fatal cases from the EEA have been received. Five cases had severe underlying diseases with the causes of death being lung oedema and pneumonia, pulmonary haemorrhage, acute respiratory syndrome (with nasal and throat swabs positive for influenza A/H1N1 infection), myocardial infarction and cardiovascular arrest. One patient died from anaphylactic shock linked to an antibiotic and another patient died following administration of either Pandemrix or Focetria with unknown latency. No additional information is available for this last case.
- The most frequently reported suspected adverse reactions in children since authorisation include pyrexia, hyperpyrexia, vomiting, injection-site pain, diarrhoea, headache, cough, fatigue, rash, decreased appetite, abdominal pain, nausea, malaise, listlessness, injection-site erythema, somnolence, crying, injection site swelling, pallor, dyspnoea, influenza-like illness, myalgia, pain in extremity and tearfulness.
- All reports of haematopoietic cytopenia (a low number of cells in the blood) received by EudraVigilance since authorisation have been reviewed. Of the 23 cases retrieved, 15 described the occurrence of thrombocytopenia (with no other cytopenia). The issue of thrombocytopenia has already been discussed in the sixth update. Six reports described a decrease in the number of

white blood cells (leucopenia, granulocytopenia, neutropenia, lymphocytopenia and agranulocytosis). In five of these cases, the patient had an underlying infection or another condition, or was taking medication that could provide an alternative explanation for the event. One case of leucopenia lacked sufficient information to allow assessment. The two remaining reports included one case of transient erythroblastopenia of childhood (TEC) – a slowly developing anaemia seen in early childhood - and one case of pancytopenia. For the latter case, another drug known to be associated with this event was primarily suspected. Overall, alternative explanations for the adverse events exist for seven of the eight cases. The absence of baseline haematological values prior to vaccination precludes a detailed or meaningful causality assessment for these cases.

- Since authorisation, five reports of an increased number of white cells in the blood have been received by EudraVigilance. They concern two cases of lymphocytosis and three cases of leucocytosis that were not specified further. All cases were in possible temporal association with vaccination but baseline white blood cell counts were not documented. Moreover, one case is not assessable due to a lack of information, one case was associated with recurring epistaxis (further evaluation is ongoing), one case had pre-existing leucocytosis, one case of lymphocytosis was associated with chronic obstructive pulmonary disease, and one case of mild leucocytosis was associated with facial palsy. There is no indication of an association between any of these cases and the vaccine.
- Nine reports of diabetes mellitus have been notified to EudraVigilance. Five reports describe the loss of control of pre-existing diabetes at varying times after vaccination, one report concerns a case of gestational diabetes mellitus that has not been confirmed medically, and three reports concern new-onset diabetes mellitus in children, with a delay of onset ranging from a few days to a few weeks after vaccination. Diabetes mellitus is a common medical condition and no conclusions can be drawn from the small number of cases reported or from uncontrolled cases in temporal relationship with Pandemrix.
- Two cases of systemic lupus erythematous rash in temporal association with vaccination have been received. One case, considered to be non-serious, describes a flare of pre-existing systemic lupus erythematosus in a polymedicated 70-year-old woman two days after vaccination. The other case concerns a 54-year-old woman who developed a lupus-like rash with positive antinuclear antibodies three days after the second dose of Pandemrix. The patient was also receiving a drug that is known to be associated with subacute cutaneous lupus erythematosus or lupus-like syndrome. These cases do not suggest that Pandemrix contributes towards the occurrence of systemic lupus erythematous rash.
- Three reports of bullous dermatitis reported since authorisation have been reviewed. They concern one poorly documented case considered to be non-serious, one case associated with herpes zoster and one case of suspected erythema multiforme for which further tests are ongoing. These three cases do not raise any concerns. All reported cases of serious skin reactions will remain under close monitoring.

A/H1N1 vaccine without a brand name in the report

From the beginning of the vaccination campaigns to 17 January 2010, 825 reports from the EEA were received in EudraVigilance without the brand name of the pandemic vaccine. The names of the suspected vaccine given included terms such as 'swine flu vaccine', 'pandemic vaccine' or 'A/H1N1 vaccine'. Many of these cases were reported directly by patients to national competent authorities using web-based reporting systems before being transferred to EudraVigilance. The distribution of these reports by SOC closely matches that of the other centrally authorised vaccines.



- The most frequently reported suspected adverse reactions experienced by patients by SOC were as follows:
  - Gastrointestinal disorders: nausea, diarrhoea, vomiting, lip swelling, abdominal pain, abdominal discomfort/pain upper;
  - General disorders and administration-site conditions: pyrexia, hyperpyrexia, injection site pain, fatigue, influenza-like illness, oedema peripheral, chills;
  - Musculoskeletal: myalgia, pain in extremity, arthralgia, musculoskeletal stiffness;
  - Nervous-system disorders: headache, dizziness, paraesthesia, crying, tremor, hypoaesthesia, somnolence;
  - Psychiatric disorders: insomnia, head banging, hallucination;

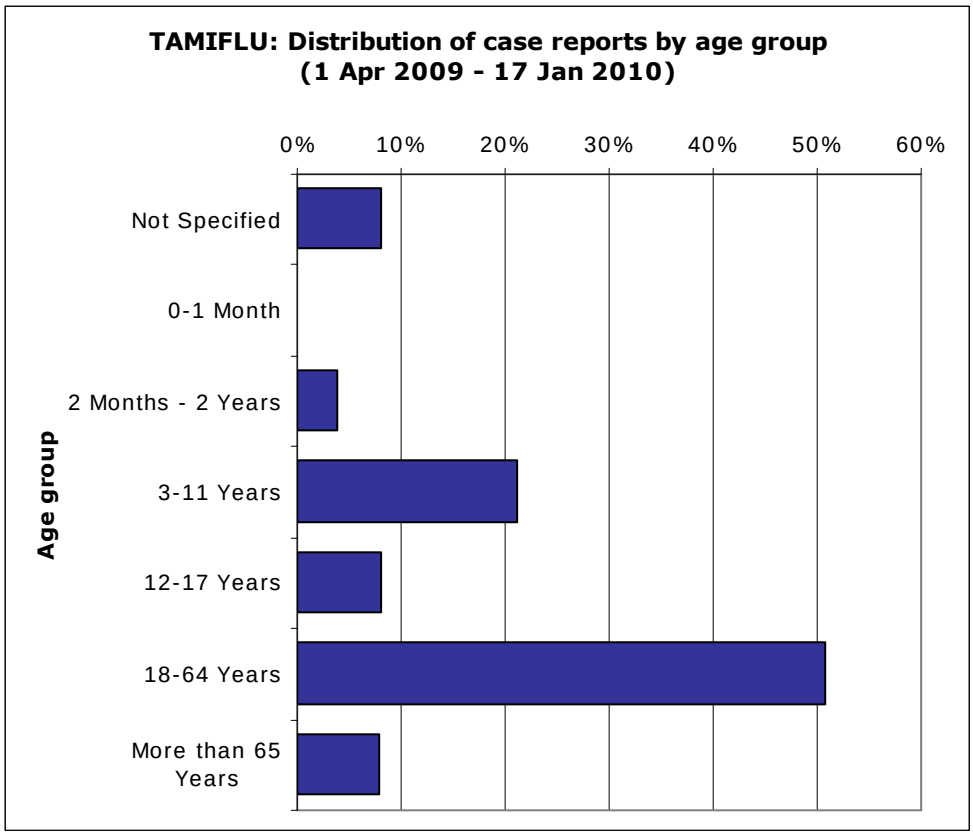
  - Respiratory, thoracic and mediastinal disorders: cough, oropharyngeal pain, dyspnoea, dry throat;
  - Skin and subcutaneous conditions: rash, hyperhidrosis, erythema, pruritus generalised, pruritis, urticaria.

- The adverse reactions included in these reports are consistent with the safety profiles described in the product information for the vaccines authorised in the EU. The European Medicines Agency encourages the marketing authorisation holders and national competent authorities to take all necessary steps to contact the primary sources of these reports so that further information can be obtained to enable the identification of the vaccines administered.

Antiviral medicines

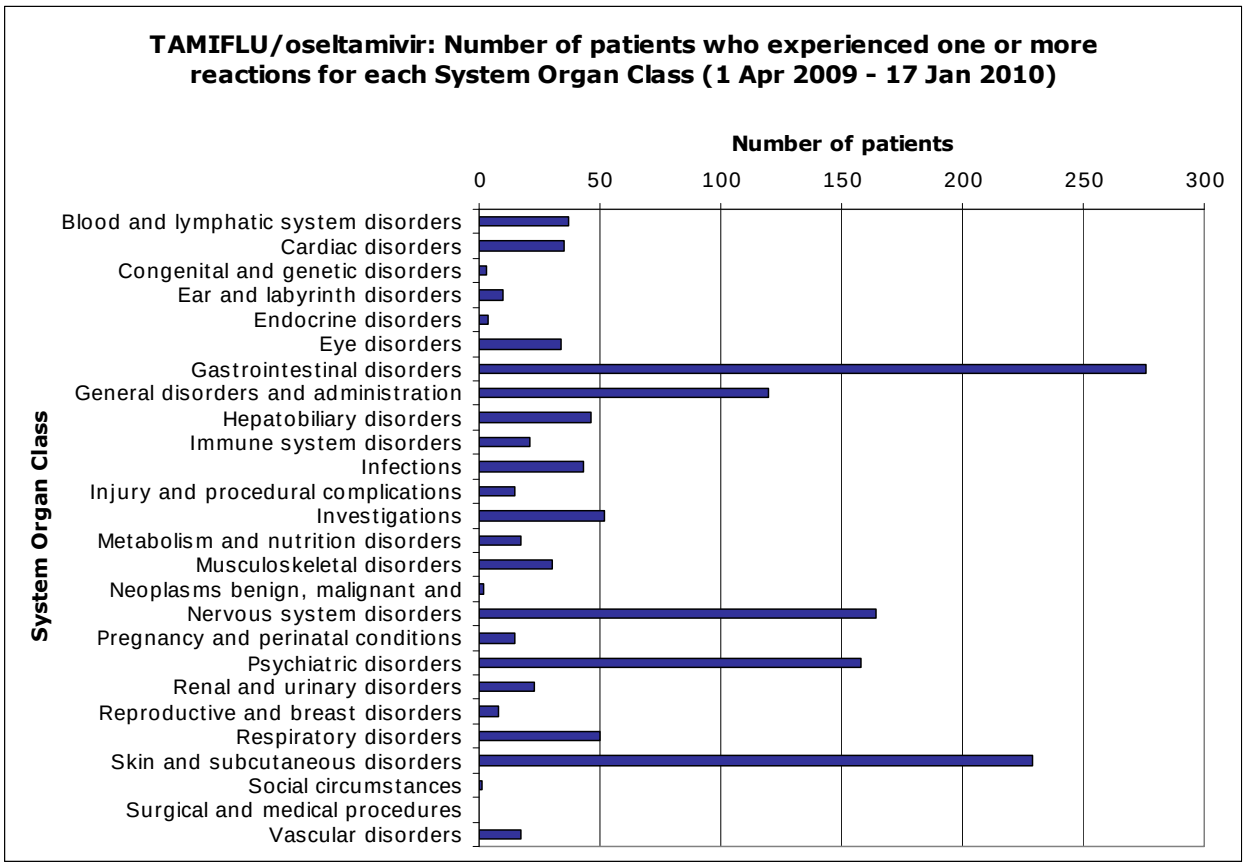
Tamiflu (oseltamivir)

From 1 April to 17 January 2010, a total of 947 reports worldwide were received by EudraVigilance (an increase of 14 reports since the previous update). The graph below displays the age distribution of patients who experienced an adverse reaction reported to EudraVigilance.



According to the information received from the marketing-authorisation holder dated 23 December 2009, exposure to Tamiflu is estimated to be 16.4 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, pruritus, rash pruritic, rash macular, angioedema;
  - Nervous-system disorders: headache, convulsion, paraesthesia, dizziness, tremor, syncope, cardiovascular accident, nystagmus, epilepsy, burning sensation, dysgeusia;
  - 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, chest pain, oedema peripheral, pyrexia, 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, alanine aminotransferase increased, gamma-glutamyltransferase increased, hepatic enzyme increased, prothrombin time prolonged;

  - Respiratory disorders: epistaxis, dyspnoea, chronic obstructive pulmonary disease;
  - Hepatobiliary disorders: hepatitis, hepatic failure, acute hepatic failure, hepatotoxicity.

- Since the last update, 11 case reports worldwide have been received by the EudraVigilance system with a fatal outcome following oseltamivir use. All of these occurred outside the EEA. In eight of the cases, the death was related to pneumonia or influenza. In two of the cases, the death was due to cardiac failure reported as not being related to oseltamivir, and in one case each, peripartum cardiomyopathy, morbid obesity, pneumonia and drug abuse were reported as contributing to the death.
- The most frequent suspected adverse reactions reported in children since the beginning of the pandemic in April 2009 are vomiting, rash, hallucination, confusional state, nightmare, epistaxis, headache, urticaria, convulsion, diarrhoea, nausea and abdominal pain.

Appendix

Specific topics discussed for H1N1 vaccines in previous updates

	Celvapan	Focetria	Pandemrix
1st Update		Cerebral haemorrhage	Fever, local reaction and drowsiness following 2nd dose in children 6-35 months old Pregnancy-related events Anaphylactic reactions in children Guillain-Barré syndrome Heart transplant rejection
2nd Update	Paraesthesia Anaphylaxis, angioedema, hypersensitivity	Pregnancy-related events Guillain-Barré syndrome	Anaphylactic shock Pregnancy-related events Transplant rejection
3rd Update	Circulatory collapse	Anaphylactic shock Acute disseminated encephalomyelitis (ADEM) Encephalitis	Transplant rejection Injection site necrosis Guillain-Barré syndrome Paralysis and paresis Cerebral infarction
4th Update	Guillain-Barré syndrome Eye disorders	Guillain-Barré syndrome Facial palsy Intra-uterine death	Guillain-Barré syndrome Idiopathic thrombocytopenic purpura (ITP) Sudden hearing loss Seizures with fatal outcome Delayed hypersensitivity reaction type IV
5th Update	Guillain-Barré syndrome	Guillain-Barré syndrome Multiple sclerosis Cardiovascular accidents Leukocytoclastic vasculitis Encephalitis	Guillain-Barré syndrome Multiple sclerosis
6th Update		Thrombocytopenia	Guillain-Barré syndrome Peripheral neuropathy Vasculitis ITP Necrotising pharyngitis and necrotising stomatitis Serum sickness
7th Update	Medication error Eye disorders	Eye disorders	Medication error Facial palsy

	Paresis, paralysis, monoplegia, diplegia Acute pancreatitis		Eye disorders Photophobia

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