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Patient Health Protection

Fifth pandemic pharmacovigilance weekly update

This update has been prepared by the European Medicines Agency to provide a summary of the adverse drug reactions reported after use of centrally authorised pandemic vaccines and antivirals. It also provides information on the evolution of the H1N1 pandemic, an estimate of how many doses have been distributed or administered in Europe, and other available information on the benefits and risks of the vaccines and antivirals. The centrally authorised pandemic medicines concerned by this update are the vaccines Celvapan, Focetria and Pandemrix and the antiviral Tamiflu.

This update includes reports of *suspected* reactions that were observed after the medicines were administered. This does not mean that these reactions have been caused by the medicine. They could be a symptom of another illness or they could be associated with another product taken by the patient. Healthcare professionals are actively encouraged to report suspected adverse reactions occurring after vaccination.

It should be noted that, due to differences in the numbers of persons having received each vaccine, the number of reports shown for the three different vaccines cannot be used for a comparison between them regarding safety or benefit-risk balance.

Reports are collected on a continuous basis in EudraVigilance. EudraVigilance is a database and management system managed by the European Medicines Agency for the collection and evaluation of reports of suspected adverse drug reactions to medicinal products. It allows the transfer of reports from national regulatory agencies and marketing authorisation holders to the European Medicines Agency, and the early detection and monitoring of possible safety signals in relation to reported adverse reactions. This update includes reports received in EudraVigilance up to 27 December 2009.

A list of the most frequently reported suspected adverse reactions is presented for the organ systems with the largest number of reports. A single patient may experience several reactions that will be included in a single report. Therefore the number of reactions may not be equal to the number of patients. As some patients have received two doses of the vaccine, the number of doses administered is not equal to the number of vaccinated patients.

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Key messages

At least 29.4 million persons including at least 218,000 pregnant women have been vaccinated to-date in Europe with one of the three centrally-authorised vaccines (Celvapan, Focetria or Pandemrix). When the information available for two nationally-authorised vaccines (Panenza and Fluval P) is considered at least 32.7 million persons have been vaccinated in Europe. A fraction of these persons have received two doses of the vaccine, but this percentage varies across countries.

The vast majority of adverse reactions that have been reported are considered non-serious.

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

There is no evidence of a causal relationship between the H1N1 vaccination and the occurrence of a new episode or a relapse of multiple sclerosis. A review of all possible cases of multiple sclerosis reported up to 27 December for the 3 vaccines has identified a total of 11 reports of suspected multiple sclerosis in patients vaccinated with Focetria (2 cases) and Pandemrix (9 cases). As explained below, the review has identified no causal association between these cases and the vaccination. This issue will be kept under close monitoring.

An update regarding the number of cases of Guillain-Barré syndrome reported up to 27 December has shown that a total of 19 cases have been reported so far in patients vaccinated with Celvapan (1), Focetria (4) and Pandemrix (14). Taking into account the number of patients vaccinated with one of the three vaccines and the background incidence rate of Guillain-Barré syndrome, the number of reported cases is lower than the number of cases that is expected to occur naturally in the vaccinated population. Every new case will be carefully evaluated and closely followed.

For further information on the established adverse reactions included in the authorised product information for centrally authorised pandemic vaccines (Celvapan, Focetria, Pandemrix) and antivirals (Tamiflu), visit the Agency's Pandemic influenza (H1N1) website.

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

Pandemic information

According to the European Centre for Disease prevention and Control (ECDC) (for latest report click through here), as of January 4th, a total of 1,934 pandemic influenza deaths have been reported since April 2009. While most deaths have to date been in Western Europe there are increasing numbers of deaths being reported from Central and Eastern Europe. The reported cumulative fatal pandemic (H1N1) cases in the world have now passed 10,000 cases. However, because of lack of laboratory confirmation and underreporting (among other factors), this is likely to be a gross underestimation of the true number of fatalities associated with the pandemic.

In its Weekly influenza surveillance overview of 24 December 2009 and its Executive Update, the ECDC concluded that most countries are witnessing medium influenza intensity with only two reporting high levels. In the majority of countries, activity is still widespread. Only one country reported an increasing trend in consultations for influenza-like illness or acute respiratory infection, and, of the other 19 countries that reported epidemiological data in the week of 14-20 December 2009, 17 reported a declining trend and two reported stable levels. Fourteen countries reported observing a decline for two weeks in succession. While the proportion of influenza-positive sentinel samples continued to decline, the 2009 pandemic influenza A(H1N1) virus still accounted for 99% of all subtyped viruses in sentinel

patients and for 98% in patients with severe acute respiratory infection (SARI). One in five SARI cases had no known underlying medical condition.

See also the ECDC pandemic website and its current Risk Assessment for additional information.

In its Weekly Update dated 30 December, the World Health Organisation states that, as of 27 December 2009, worldwide more than 208 countries and overseas territories or communities have reported laboratory confirmed cases of pandemic influenza H1N1 2009, including at least 12,220 deaths.

Overview of centrally authorised vaccines

As of 27 December 2009, a total of 11,126 reports had been received by EudraVigilance since the authorisation of the three centrally-authorised vaccines. This represents an increase of 2,381 reports compared with the previous update. This reflects the increase in the number of vaccinated people.

Data available on 4 January 2010 from Member States and from the companies indicate that at least 95.8 million doses have been distributed and at least 29.4 million patients have been vaccinated in the EEA with one of the three centrally-authorised vaccines. From limited information received from 7 EEA countries by 4 January 2010, at least 218,000 pregnant women have been vaccinated.

When the information available for two nationally-authorised vaccines (Panenza and Fluval P) is considered, at least 100 million doses have been distributed, with at least 32.7 million persons (including at least 252,000 pregnant women) vaccinated in Europe.

A review of cases of multiple sclerosis reported up to 27 December for the three vaccines identified a total of 11 cases reported in patients vaccinated with Focetria (2 cases) and Pandemrix (9 cases). Nine of the 11 cases concerned patients who experienced a relapse or an aggravation of a pre-existing multiple sclerosis after intervals ranging from 2 hours to 2 weeks after the vaccination. Multiple sclerosis relapses are often unpredictable. Viral infections such as common cold, influenza, or gastroenteritis are known to increase the risk of relapse, but there is no evidence that vaccination may be a trigger. Two new cases of multiple sclerosis were reported to have developed at 3 hours and 2 weeks following vaccination with Pandemrix, but such a short time for developing the disease does not indicate a plausible relationship with the vaccination. As the first symptoms of the disease may not be reported with a diagnosis of multiple sclerosis, the Eudravigilance database was searched for terms representing early onset of multiple sclerosis. Isolated cases of trigeminal neuralgia, optic neuritis, transverse myelitis and acute disseminated encephalomyelitis were found, but without any common pattern that could point towards a relationship with the vaccine. The incidence of new-onset multiple sclerosis varies by age, gender and country, and the number of cases reported up to now in vaccinated patients is much lower than the expected number of cases that would naturally occur. There is currently no evidence that the vaccines could be related to the development of multiple sclerosis. This issue will be kept under close monitoring.

A review of cases of Guillain-Barré syndrome (GBS) received for Celvapan, Focetria and Pandemrix has been presented in the fourth Update. Six additional reports have been received since the fourth update: 1 in relation to Focetria and 5 in relation to Pandemrix. The case reported in relation to Focetria concerns a woman who experienced “stomach flu” one hour after the vaccination and symptoms of GBS one week later. She had also received a seasonal influenza vaccine two weeks before the vaccination with Focetria. There is no evidence that Focetria was the cause of GBS. Amongst the 5 reports received in relation to Pandemrix, the diagnosis has not been confirmed in 3 cases, demyelinating asymptomatic lesions were suspected to be present before the vaccination in 1 case, and a 15-year old male patient presented with GBS 23 days after the vaccination. There is no

information on past medical history in this case and investigations are ongoing. Since authorisation of the vaccines, a total of 19 cases have thus been reported so far in patients vaccinated with Celvapan (1), Focetria (4) and Pandemrix (14). The conclusion of the fourth update still apply: several factors are known to play a role in the occurrence of GBS; taking into account the number of patients vaccinated with one of the 3 vaccines and an overall background incidence rate of 2 cases per 100,000 persons and per year, the number of cases reported in relation to the pandemic vaccines is lower than the number of cases that is expected to occur naturally in the vaccinated population. However, every new case will be closely reviewed and followed.

Celvapan

As of 27 December 2009, a total of 356 reports had been received in EudraVigilance (increase of 105 reports since the previous update). According to company [1] and Member State information, a total of 6,006,000 doses had been distributed to EEA countries up to 29 December 2009. It is estimated that at least 260,000 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 experienced by patients in each System Organ Class since the authorisation of the vaccine are:
  - Nervous system disorders: headache, dizziness, syncope, paraesthesia, hypoaesthesia;
  - General disorders and administration site conditions: pyrexia, malaise, chills, fatigue, asthenia, feeling hot, influenza-like illness;
  - Gastrointestinal disorders: nausea, vomiting, diarrhoea, abdominal pain
  - Musculoskeletal disorders: myalgia, arthralgia, pain in extremity, muscular weakness;
  - Skin and subcutaneous conditions: hyperhidrosis, pruritus, urticaria, rash, erythema;
  - Respiratory disorders: oropharyngeal pain, dyspnoea, cough;
  - Vascular disorders: pallor, flushing, hypotension;
  - Immune disorders: hypersensitivity, anaphylactic reaction.

Updated safety information

- The most frequently suspected adverse reactions reported in children since authorisation include hypersensitivity, vomiting, syncope, pyrexia, dizziness, nausea, pallor, headache, rash, vision blurred, hyperhidrosis, cough.
- Since the last update, no fatal case has been reported from the EEA in relation to Celvapan.

Focetria

As of 27 December 2009, a total 2,641 reports had been received in EudraVigilance (increase of 402 reports since the previous update). Data available on 4 January 2010 from Member States and from

[1] As stated by the marketing authorisation holder in the simplified Periodic Safety Update Report (S-PSUR) dated 23 December 2009.

the company [2] indicate that at least 28 million doses of Focetria had been distributed in the EEA, and at least 7.5 million individuals had been vaccinated.

Distribution of adverse reactions by System Organ Class

- In reports received from the EEA, the most frequent suspected adverse reactions experienced by patients in each SOC since the authorisation of the vaccine are:
  - General disorders and administration site conditions: pyrexia, fatigue, injection site pain, influenza-like illness, malaise, chills, injection site erythema, hyperpyrexia, injection site swelling, chest pain;
  - Nervous system disorders: headache, dizziness, paraesthesia, dysgeusia, somnolence, tremor, presyncope, syncope, hypoaesthesia, convulsion, migraine;
  - Musculoskeletal disorders: myalgia, pain in extremity, arthralgia, musculoskeletal stiffness, neck pain, muscular weakness, back pain, muscle spasms, musculoskeletal pain, sensation of heaviness;
  - Gastrointestinal disorders: nausea, diarrhoea, vomiting, abdominal pain, abdominal discomfort;
  - Skin and subcutaneous conditions: rash, pruritus, urticaria, erythema, hyperhydrosis, rash pruritic, dermatitis allergic, angioedema, swelling face, rash generalised;
  - Respiratory disorders: cough, dyspnoea, oropharyngeal pain, bronchospasm, dysphonia;
  - Infections: rhinitis, nasopharyngitis, pneumonia, pharyngitis, influenza, herpes zoster.

Updated safety information

- The most frequently reported suspected adverse reactions in children since authorisation include pyrexia, hyperpyrexia, headache, vomiting, cough, nausea, abdominal pain, diarrhoea, injection site pain, myalgia, influenza-like illness, rash, dyspnoea, urticaria.
- Since the last update, 4 cases with a fatal outcome have been received from the EEA. The four patients had severe pre-existing conditions which were more likely the cause of death than the vaccination (type II diabetes with severe renal impairment, myocardial infarction, severe chronic obstructive pulmonary disease, hypertension).
- From authorisation to 27 December 2009, 6 reports mentioned that a severe cardiovascular accident occurred in vaccinated patients. The events included cerebral haemorrhage, embolic cerebral infarction and cerebral infarction. All patients had previous clinical history of cardiovascular accidents or suffered from related conditions such as hypertension. There is therefore no reason to suspect that the vaccine was the cause of the cardiovascular accident in these patients. One case of acute coronary syndrome was also received, however, the patient had a previous history of angina.
- Two cases of leukocytoclastic vasculitis were received. Both were evaluated as non-serious by the health professional who reported them. One patient had a history of cardiovascular disorders and the other one suffered from diverticulitis. There is currently not evidence for an association between the vaccine and the occurrence of leukocytoclastic vasculitis.

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

- A review of cases of encephalitis received with Focetria was performed. Six cases were identified, 3 of which were received since the last update. The age of these patients varied widely, from 8 to 77 years. Although these cases are being investigated further, initial analysis suggests that there is not grounds to believe that the vaccine was the cause of the encephalitis.

Pandemrix

As of 27 December 2009, a total of 8,129 reports had been received in EudraVigilance (increase of 1,874 reports since the previous update). Data available on 4 January 2009 from Member States and from the company [3] indicate that at least 61.7 million doses of Pandemrix had been distributed in the EEA. It is estimated that at least 21.6 million individuals have been vaccinated.

Distribution of adverse reactions by System Organ Class

- In reports received from the EEA, the most frequent suspected adverse reactions experienced by patients in each SOC since the authorisation of the vaccine are:
  - General disorders and administration site conditions: pyrexia, hyperpyrexia, injection site pain, fatigue, influenza-like illness, malaise, chills, injection site swelling, injection site erythema, oedema peripheral, pain;
  - Nervous system disorders: headache, dizziness, paraesthesia, somnolence, syncope, hypoaesthesia, crying, lethargy, convulsions, tremor;
  - Gastrointestinal disorders: vomiting, nausea, diarrhoea, abdominal pain, paraesthesia oral, lip swelling, swollen tongue, dry mouth, abdominal discomfort, hypoaesthesia oral;
  - Musculoskeletal disorders: myalgia, pain in extremity, arthralgia, musculoskeletal stiffness, muscular weakness, back pain, limb discomfort, musculoskeletal pain, neck pain;
  - Skin and subcutaneous conditions: rash, erythema, urticaria, hyperhydrosis, pruritus, rash generalised, angioedema, swelling face, cold sweat, rash erythematous;
  - Respiratory disorders: cough, dyspnoea, oropharyngeal pain, hyperventilation, asthma, rhinorrhoea, wheezing, epistaxis, tachypnoea, pharyngeal oedema, bronchospasm;
  - Vascular disorders: pallor, circulatory collapse, hypotension, flushing, hypertension, hot flush, peripheral coldness;
  - Psychiatric disorders: listless, insomnia, tearfulness, sleep disorder, restlessness, nightmare;
  - Infections: rhinitis, nasopharyngitis, pneumonia, influenza, herpes zoster;
  - Immune disorders: anaphylactic reaction, hypersensitivity, anaphylactic shock, anaphylactoid reaction.

Updated safety information

- The most frequently suspected adverse reactions reported in children since authorisation are pyrexia, hyperpyrexia, vomiting, injection site pain, headache, diarrhoea, cough, fatigue, decreased appetite, abdominal pain, rash, nausea, malaise, listless, somnolence, injection site erythema, injection site swelling, influenza-like illness, myalgia and pain in extremity.

[3] As stated by the marketing authorisation holder in the simplified Periodic Safety Update Report (S-PSUR) dated 21 December 2009.

- Since the last update, 26 cases with a fatal outcome have been received from the EEA. The cause of death was linked to a severe cardiovascular disorder in 12 cases (e.g. myocardial infarction, acute circulatory failure, sudden cardiac death, cardiac tamponade or cardiac decompensation), to a respiratory disease in 6 cases (e.g. pneumonia, bronchopneumonia, asthma), to multiorgan failure in 2 cases and to pulmonary embolism, intestinal gangrene and AIDS (one case each). In 3 other cases, no immediate cause of death was found. They concerned a 53 years-old patient with several previous episodes of aspiration pneumopathy due to paralysis who was found dead the day after the vaccination, a 21 year-old person who suddenly died 21 days after the vaccination (autopsy has been requested) and a 54-year old woman with a medical history of hypertension and type I diabetes who suddenly died one day after the vaccination. Results of the autopsy are not known at present. In none of these cases, was a causal association between the death and the vaccine suspected.

Antiviral medicines

Tamiflu

From 1 April to 27 December 2009, a total number of 835 reports worldwide have been received in EudraVigilance (increase of 28 reports since the previous update).

According to information received from the marketing authorisation holder dated 23 December 2009, the patient exposure to oseltamivir is estimated to be 16,360,991 patients during the pandemic period from 1 May 2009 to 30 November 2009 [4].

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 frequent reported suspected adverse reactions experienced by patients in each SOC:
  - Gastrointestinal disorders: vomiting, nausea, diarrhoea, abdominal pain, mouth ulceration, lip swelling;
  - Skin and subcutaneous conditions: rash, rash generalised, urticaria, swelling face, Stevens-Johnson syndrome, pruritis, rash pruritic;
  - Nervous system disorders: headache, convulsion, paraesthesia, dizziness, tremor, cardiovascular accident;
  - Psychiatric disorders: hallucination, confusional state, nightmare, insomnia, anxiety, delirium, hallucination, visual;
  - General disorders and administration site conditions: malaise, oedema peripheral, fatigue, chest pain, drug interaction, influenza-like illness;
  - Respiratory disorders: epistaxis, dyspnoea.

[4] As stated by the marketing authorisation holder in the Pandemic Safety Report dated 23 December 2009.