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Questions and answers on the review of Pandemrix Influenza vaccine (H1N1) (split virion, inactivated, adjuvanted) A/California/7/2009 (H1N1)v like strain (X- 179A)

Outcome of a procedure under Article 20 of Regulation (EC) No 726/2004

The European Medicines Agency has completed a review of Pandemrix following concerns about a suspected link between vaccination with Pandemrix and narcolepsy in children and adolescents. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of Pandemrix continue to outweigh its risks but that it may only be used in people under 20 years of age if the recommended annual seasonal trivalent influenza vaccine is not available and if immunization against H1N1 is still needed, for instance in people at risk of the complications of infection.

What is Pandemrix?

Pandemrix is a vaccine that is given by injection, to protect against influenza (flu) caused by the A (H1N1)v 2009 virus. Pandemrix contains a flu strain called A/California/7/2009 (H1N1) v-like strain (X 179A) which has been inactivated. Pandemrix is given according to official recommendations and can only be obtained with a prescription.

Pandemrix has been authorised in the EU since September 2009. The vaccine was used extensively during the 2009 (H1N1) pandemic, with at least 30.8 million people vaccinated in the EU.

Why was Pandemrix reviewed?

The review of Pandemrix was initiated to investigate a possible link between Pandemrix vaccination and narcolepsy, following an increased number of reported cases of narcolepsy among children and adolescents in Finland and Sweden following the H1N1 pandemic vaccination campaign in late 2009 and early 2010. The current review has been conducted in the context of seasonal use.

Narcolepsy is a rare sleep disorder (with around 10 new cases per million people every year) that causes a person to fall asleep suddenly and unexpectedly, characterised by excessive daytime sleepiness, sometimes accompanied by sudden episodes of muscle weakness (cataplexy). The exact



cause of narcolepsy is currently unknown. It is generally considered to be triggered by genetic and environmental factors including infections.

The reported cases of narcolepsy followed the H1N1 pandemic vaccination campaign in late 2009 and early 2010. On 24 August 2010, Finland's National Institute for Health and Welfare recommended that vaccination with Pandemrix be discontinued until the suspected link with narcolepsy was thoroughly evaluated. On 27 August 2010 the European Commission asked the CHMP to issue an opinion on Pandemrix and on whether its marketing authorisation should be maintained, varied, suspended or withdrawn across the EU.

During the review, further data from epidemiological (population-based) studies in Sweden and France became available suggesting a link between Pandemrix and narcolepsy. In April 2011, the CHMP decided that Pandemrix could not be ruled out as a contributor to an increased risk of narcolepsy and that interim measures should be taken pending the final outcome of the review. It recommended that the product information be amended to advise prescribers to take into account the early results from epidemiological studies, and to assess the risks and potential benefits for individuals when considering the use of Pandemrix in children and adolescents¹.

Which data has the CHMP reviewed?

The CHMP considered all the available data on the possible association between Pandemrix and narcolepsy and the impact on the overall benefit-risk balance of Pandemrix. These included the results of epidemiological studies carried out in Finland and Sweden, an analysis of safety surveillance data performed in several EU Member States and, case reports from the across the EU. They also included the preliminary results of an epidemiological study of narcolepsy and pandemic vaccines in eight EU Member States, coordinated by the European Centre for Disease Prevention and Control (ECDC) through a network of research and public health institutions (VAESCO)².

The CHMP also took advice from a specially convened meeting of experts in fields such as paediatric neurology, vaccinology, immunology, sleep disorders, infectious diseases, epidemiology, as well as Health Canada, the World Health Organisation (WHO) and the ECDC, to consider the latest available data regarding the possible link between Pandemrix and narcolepsy.

What are the conclusions of the CHMP?

The CHMP considered that the epidemiological studies relating to Pandemrix in Finland and Sweden were well designed and show an association between Pandemrix vaccination and narcolepsy in children and adolescents in those countries. The results indicate a six to 13-fold increased risk of narcolepsy in vaccinated as compared with unvaccinated children and adolescents, corresponding to about three to seven additional cases in every 100,000 vaccinated subjects. The increased risk was not seen in adults (older than 20 years). A similar risk has not been confirmed but cannot be ruled out in other countries.

The Committee noted that the vaccine is likely to have interacted with genetic or environmental factors which might raise the risk of narcolepsy, and that other factors may have contributed to the results.

There are several initiatives being developed across the EU to further investigate this association. The CHMP noted that similar epidemiological studies have not been completed in other countries. The preliminary results of the VAESCO study confirmed the signal in Finland, while the available results do not allow for conclusions in other EU countries (where vaccination coverage with Pandemrix was

¹ See the press release at:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/04/news_detail_001244.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1

² More information about the VAESCO network of research and public health institutions can be found on their [website](#).

lower). The final results of the VAESCO study are still awaited. Exposure to specific infectious diseases (including H1N1) at different ages, particularly upper respiratory infections, may have contributed to the observations in the Nordic area. The CHMP considered that it would be helpful if ongoing epidemiological studies seek to address this question. The CHMP stressed that further research is necessary.

Based on the evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that Pandemrix may only be used in people under 20 years of age if the recommended annual seasonal trivalent influenza vaccine (which protects against 3 influenza strains) is not available and if immunization against H1N1 is still needed. The CHMP recommended that the product information for Pandemrix be updated accordingly.

The marketing authorisation holder for Pandemrix is carrying out a retrospective cohort study in Canada, where an equivalent H1N1 vaccine (Arepanrix) was widely used. The company has committed to carry out non-clinical and clinical studies to further explore the association between Pandemrix vaccination and narcolepsy.

What are the recommendations for patients and healthcare professionals?

- Healthcare professionals may only use Pandemrix in people under 20 years of age if the recommended annual seasonal trivalent influenza vaccine is not available and if immunization against H1N1 is still needed, for instance in people at risk of the complications of infection.
- Patients who have already received the Pandemrix vaccine do not need to take any action.
- Any patient (whether vaccinated or not) experiencing narcoleptic symptoms, such as unexplained excessive daytime sleepiness, is advised to consult a doctor to discuss their symptoms at a routine appointment.
- Patients who have any questions should speak to their doctor or pharmacist.

A European Commission decision on this opinion will be issued in due course.

The current European public assessment report for Pandemrix can be found on the Agency's website: ema.europa.eu/Find_medicine/Human_medicines/European_Public_Assessment_Reports.