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HPV vaccines: EMA confirms evidence does not support that they cause CRPS or POTS

Reports after HPV vaccination consistent with what would be expected in this age group

On 19 November EMA completed its review of the evidence surrounding reports of two syndromes, complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS) in young women given human papillomavirus (HPV) vaccines. These vaccines are given to protect them from cervical cancer and other HPV-related cancers and pre-cancerous conditions. In line with its initial recommendations, EMA confirmed that the evidence does not support a causal link between the vaccines (Cervarix, Gardasil/Silgard and Gardasil 9) and development of CRPS or POTS. Therefore there is no reason to change the way the vaccines are used or amend the current product information.

CRPS is a chronic pain syndrome affecting a limb, while POTS is a condition where the heart rate increases abnormally on sitting or standing up, together with symptoms such as dizziness, fainting and weakness, as well as headache, aches and pains, nausea and fatigue. In some patients they can severely affect the quality of life. The syndromes are recognised to occur in the general population, including adolescents, regardless of vaccination.

Symptoms of CRPS and POTS may overlap with other conditions, making diagnosis difficult in both the general population and vaccinated individuals. However, available estimates suggest that in the general population around 150 girls and young women per million aged 10 to 19 years may develop CRPS each year, and at least 150 girls and young women per million may develop POTS each year. The review found no evidence that the overall occurrence of these syndromes in vaccinated girls were different from expected occurrence in these age groups, even taking into account possible underreporting. The review noted that some symptoms of CRPS and POTS may overlap with chronic fatigue syndrome (CFS, also known as myalgic encephalomyelitis or ME). Many of the reports considered in the review have features of CFS and some patients had diagnoses of both POTS and CFS. Results of a large published study that showed no link between HPV vaccine and CFS were therefore particularly relevant.

The Agency's review included published research, data from clinical trials and reports of suspected side effects from patients and healthcare professionals, as well as data supplied by Member States. The Agency's Pharmacovigilance Risk Assessment Committee (PRAC) was responsible for the initial review. In reaching its recommendations, it also consulted a group of leading experts in the field, and took into

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account detailed information received from a number of patient groups that also highlighted the impact these syndromes can have on patients and families.

The findings of the PRAC were passed to the Agency's Committee for Medicinal Products for Human Use (CHMP), along with further representations from patient groups. The CHMP concurred that the available evidence does not support that CRPS and POTS are caused by HPV vaccines. It therefore did not recommend any changes to the terms of licensing or the product information for these medicines.

The review recognised that more than 80 million girls and women worldwide have now received these vaccines, and in some European countries they have been given to 90% of the age group recommended for vaccination. Use of these vaccines is expected to prevent many cases of cervical cancer (cancer of the neck of the womb, which is responsible for over 20,000 deaths in Europe each year) and various other cancers and conditions caused by HPV. The benefits of HPV vaccines therefore continue to outweigh the known side effects. The safety of these vaccines, as with all medicines, will continue to be carefully monitored and will take into account any future new evidence of side effects that becomes available.

The CHMP's position was passed to the European Commission which endorsed it and issued a legally binding decision. The assessment report containing the evidence supporting the Agency's review is available on EMA's website.

Information for patients

- HPV (human papillomavirus) is a major cause of cancer of the cervix (neck of the womb) and some other cancers, as well as other conditions such as genital warts. HPV vaccines are expected to prevent many cases of such conditions.
- There have been reports of two syndromes, CRPS and POTS, in girls who have been given HPV vaccines. CRPS produces long-lasting pain affecting a limb, and POTS is associated with an increase in heart rate on standing up, together with various symptoms including dizziness, weakness, pain, feeling sick, and fatigue. It is recognised that in some affected girls these syndromes can be long lasting and severely impact quality of life.
- CRPS and POTS are difficult to diagnose. They have been reported in the general population since before HPV vaccines became available. Symptoms often overlap with other conditions such as chronic fatigue syndrome.
- A careful review looking at the available evidence has concluded that the occurrence of CRPS and POTS in vaccinated girls is no higher than would be expected in girls in the general population (around 150 cases of CRPS and at least 150 of POTS per million each year), and that there is no evidence that the vaccines can trigger these syndromes. The review took into account cases not reported as CRPS and POTS but with signs and symptoms suggestive of these conditions.
- There are therefore no recommendations to change the way in which the vaccines are used and no changes have been made to the prescribing information for these vaccines.
- Patients or families who have any concerns should consult their healthcare professional.

Information for healthcare professionals

- Routine surveillance of suspected adverse reaction reports has raised questions on the potential association between the use of HPV vaccines and two syndromes, CRPS and POTS.

- CRPS (chronic regional pain syndrome) is defined as continuing pain that is disproportionate to the inciting event (typically an episode of trauma or limb immobilisation), and is associated with sensory, sudomotor, motor and dystrophic changes. It is usually confined to a single limb.
- Patients with POTS (postural orthostatic tachycardia syndrome) typically show abnormal increases in heart rate on standing, without orthostatic hypotension. These are accompanied by symptoms (e.g. light-headedness, syncope, weakness, headaches, chronic aches and pains, gastrointestinal symptoms and fatigue) which differ between patients.
- Symptoms, in particular of POTS, may overlap with other conditions such as chronic fatigue syndrome, and patients may have a diagnosis of both chronic fatigue syndrome and POTS.
- Available estimates suggest that in the general population around 150 girls and young women per million aged 10 to 19 years may develop CRPS each year and at least 150 girls and young women per million may develop POTS each year.
- The review found no evidence that the overall occurrence of these syndromes in vaccinated girls was different from that expected in these age groups, even taking into account a variety of possible scenarios for underreporting and reports that did not fully meet diagnostic criteria for these syndromes. Given that many reports have features of chronic fatigue syndrome, evidence including a large published study[1] that showed no link between chronic fatigue syndrome and HPV vaccines was also considered relevant.
- There are therefore no recommendations to amend the product information or to change the way HPV vaccines are used. The benefits of HPV vaccines continue to outweigh their risks. Use of these vaccines is expected to prevent many cases of cervical cancer as well as various other cancers and conditions caused by HPV.

The above recommendations are based on analyses of clinical trial and post-marketing data and included review of published literature, spontaneous reports of suspected adverse effects, reports submitted by Member States as well as information from other countries, and information submitted voluntarily by the public. The Agency also consulted a group of experts in these syndromes and in neurology, cardiology and pharmacoepidemiology.

More about the medicine

HPV vaccines are available in the European Union under the names Gardasil/Silgard, Gardasil 9, and Cervarix. Gardasil has been authorised since September 2006, and is approved for use in males and females for preventing precancerous growths and cancer in the cervix and anus, and genital warts. It contains antigens (proteins that help product antibodies) against 4 types of HPV (types 6, 11, 16 and 18). Gardasil 9 (approved in June 2015) is used similarly but contains antigens for 9 types of the virus (types 6, 11, 16, 18, 31, 33, 45, 52 and 58). Cervarix has been approved since September 2007 for use in women and girls to protect against precancerous growths and cancer in the cervix and genital area. It contains antigens for types 16 and 18 of the virus. Following their approval, the vaccines have been introduced in national immunisation programs in many countries. It is estimated that more than 63 million girls and women worldwide have been vaccinated with Gardasil/Silgard and more than 19 million with Cervarix.

[1] Donegan K, et al. Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK. *Vaccine* 2013; 31: 4961-7.

More about the procedure

The review of HPV vaccines was initiated on 9 July 2015 by the European Commission at the request of Denmark, under Article 20 of Regulation (EC) No 726/2004.

The review was first carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations. The PRAC recommendations were sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which adopted the Agency's final opinion. The final stage of the review procedure was the adoption by the European Commission of a legally binding decision applicable in all EU Member States on 12/01/2016.

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