

## **Annex**

### **Scientific conclusions**

## Scientific conclusions

Human papillomavirus (HPV) vaccines have been authorised in the European Union since 2006 for the prevention of cervical and various other cancers caused by HPV infection. Routine surveillance of suspected adverse reaction reports has raised questions on the potential association between the use of the vaccines and two syndromes in particular, which are known as Complex regional pain syndrome (CRPS) and Postural orthostatic tachycardia syndrome (POTS). These syndromes have been subject to previous repeated review by PRAC.

On 09 July 2015 the European Commission therefore triggered a procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data, and requested the EMA to assess these concerns.

The PRAC requested data and analyses from the MAHs regarding CRPS and POTS from clinical trials and post-marketing safety data, and took into account literature review, data from Eudravigilance, reports submitted by member states, including Denmark, as well as information from Japan and information submitted voluntarily by the public. The advice of the Scientific advisory group (SAG) on vaccines was sought; the expertise of this group was supplemented with additional European experts on these syndromes and on neurology, cardiology and pharmacoepidemiology.

### *CRPS*

CRPS is defined as continuing pain that is disproportionate to the inciting event and may be associated with dysautonomic signs and symptoms and is usually confined to a single limb. CRPS typically follows an episode of trauma including fracture of the wrist or carpal tunnel syndrome surgery, or immobilisation of the limb. The onset of symptoms of CRPS is difficult to define because the syndrome is usually only diagnosed from the point when normal recovery from the initiating trauma should have occurred, and is usually only recognised sometime later among those with continuing pain afterwards. 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.

In the review of clinical trial data a total of 60,594 subjects were included for Gardasil/Silgard and Gardasil 9 and 42,047 subjects for Cervarix. No cases were identified in the Cervarix and comparator cohorts. The incidence of CRPS in the Gardasil/Silgard and Gardasil 9 clinical trials was less than 1 case per 10,000 person-years and comparable in the Gardasil/Silgard and Gardasil 9 and corresponding placebo cohorts.

Analyses of observed versus expected number of spontaneous reports were undertaken, covering a wide range of scenarios regarding underreporting (from 1 – 100 % reporting) and including reports that did not fully meet the diagnostic criteria for the syndrome.

Overall, the comparisons of observed versus expected number of spontaneous reports do not suggest an increased occurrence of CRPS in relation to the HPV vaccines.

Furthermore, the detailed review of the reports of CRPS did not show a consistent pattern regarding time-to-onset (TTO) following vaccination or clinical characteristics.

The SAG also concluded that most of the reports of CRPS under review did not appear to fulfil the established diagnostic criteria for CRPS.

Overall, available data do not provide support for a causal association between HPV vaccines and CRPS.

## *POTS*

POTS is a systemic syndrome which has been known for a long time under different names and is still poorly understood. Available estimates suggest that at least 150 girls and young women per million may develop POTS each year. POTS patients typically show persistent tachycardia for more than 10 minutes upon standing, as well as an increase in heart rate to above 120 bpm or by  $\geq 30$ bpm, and in children and juveniles below 19 years of age by  $\geq 40$ bpm, without arterial hypotension. A diagnosis of POTS cannot solely rely on these criteria; other symptoms (e.g. syncope, fatigue, headaches, light-headedness, diaphoresis, tremor, palpitations, exercise intolerance, near syncope upon standing upright) vary across patients and are otherwise non-specific.

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Overall, comparisons of observed versus expected number of spontaneous reports, with the same scenarios as described above for CRPS, do not suggest an increased occurrence of POTS in relation to the HPV vaccines.

Furthermore, the detailed review of the reports did not show a consistent pattern regarding time-to-onset (TTO) following vaccination or clinical characteristics.

The vast majority of POTS reports came from a centre in Denmark (Brinth et al, 2015)<sup>1</sup>. This centre has recently published more information on these reports, suggesting that some of these individuals were likely to have had chronic fatigue syndrome (CFS). This is in accordance with the Scientific advisory group conclusions that most of the reviewed reports of POTS could better correspond to the definition of CFS or at least include some features of CFS.

A study by Donegan and colleagues (2013)<sup>2</sup>, using self-controlled case series design (and therefore avoiding the issue of differential diagnostic practice in vaccinated and unvaccinated), evaluated diagnoses of CFS, as well as referrals from general practice for as yet undiagnosed symptoms of chronic fatigue and exhaustion, as well as diagnoses for fibromyalgia, post viral syndrome and neurasthenia. The study found no association between HPV vaccine and any of the conditions studied.

Overall, available data do not provide support for a causal relation between HPV vaccines and POTS.

### *PRAC conclusions*

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 and various other cancers and conditions caused by HPV.

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

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<sup>1</sup> Brinth LS, Pors K, Theibel AC, Mehlsen J. Orthostatic intolerance and postural tachycardia syndrome as suspected adverse effects of vaccination against human papillomavirus; *Vaccine*, 2015; 33(22):2602-5.

<sup>2</sup> Donegan K, Beau-Lejdstrom R, King B, Seabroke S, Thomson A, Bryan P. Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK. *Vaccine*, 2013; 31(43): 4961-7

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 rates of these syndromes in vaccinated girls were different from expected rates in these age groups, even taking into account possible underreporting. The PRAC noted that some symptoms of these syndromes may overlap with chronic fatigue syndrome (CFS, also known as myalgic encephalomyelitis or ME). The results of a large published study<sup>2</sup> showed no link between HPV vaccine and CFS. As many of the reports considered in the review have features of CFS and some patients had diagnoses of both POTS and CFS, these results were considered relevant for the current evaluation.

Taking into account the totality of the available information the PRAC concluded that the evidence does not support that HPV vaccines (Cervarix, Gardasil, Gardasil 9, Silgard) cause CRPS or POTS. The benefits of HPV vaccines continue to outweigh their risks.

The safety of these vaccines should continue to be carefully monitored. This should include follow-up of CRPS or POTS reports to determine relevant clinical characteristics, to identify possible cases of POTS and CRPS based on broad search strategies including outcome details and to compare reporting rates against available information on the known epidemiology of POTS and CRPS.

### **Grounds for the PRAC recommendation**

Whereas,

- The Pharmacovigilance Risk Assessment Committee (PRAC) considered the procedure under Article 20 of Regulation (EC) No 726/2004 for HPV vaccines.
- The PRAC considered the totality of the data submitted with regard to a potential association between HPV vaccination and the occurrence of Complex regional pain syndrome (CRPS) and Postural orthostatic tachycardia syndrome (POTS). This included the responses submitted by the marketing authorisation holders, published literature, Eudravigilance data, and the outcome of the Scientific advisory group (SAG) on vaccines as well as data submitted by member states and information submitted by the public.
- The PRAC took note of the fact that CRPS and POTS occur in the general unvaccinated population and have been described in the medical literature before HPV vaccines were introduced.
- The PRAC considered that the observed versus expected analyses took into account a wide range of scenarios regarding underreporting and included reports that did not fully meet the diagnostic criteria for the syndromes. Overall, in these analyses the rates of these syndromes in vaccinated girls were consistent with expected rates in these age groups.
- The PRAC also noted that many of the reviewed reports of POTS had features in common with chronic fatigue syndrome (CFS). The PRAC therefore considered the results of a large published study which showed no link between HPV vaccine and CFS, as relevant for the current review.

The Committee, having considered all the information available, concluded that the evidence does not support a causal association between HPV vaccination and CRPS and/or POTS. The PRAC confirmed that the benefit-risk balance of the HPV vaccines (Cervarix, Gardasil, Gardasil 9 and Silgard) remains favourable and recommends the maintenance of the marketing authorisations.

**CHMP opinion**

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

The CHMP noted the recommendations to the MAHs that had been made by the PRAC in terms of future monitoring. It was agreed that employing broad search strategies to identify possible cases of CRPS and POTS and ongoing comparison of reporting rates against available information on the known epidemiology of CRPS and POTS is important. In this respect, the CHMP commented that these comparisons should take into account likely increasing awareness of these syndromes to ensure appropriate interpretation of emerging data.

***Overall conclusion***

The CHMP, as a consequence, considers that the benefit-risk balance of HPV vaccines (Cervarix, Gardasil, Gardasil 9 and Silgard) remains favourable and therefore recommends the maintenance of the marketing authorisations.