NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 20 OF REGULATION (EC) 726/2004
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This notification is a referral under Article 20 of Regulation (EC) 726/2004 to the PRAC made by the European Commission:

Product Name(s) Procedure name HPV vaccines	- Cervarix (Bivalent HPV vaccine (types 16, 18) - Gardasil (quadrivalent HPV vaccine (types 6, 11, 16, 18) - Gardasil 9 (9-valent HPV vaccine (types 6, 11, 16, 18, 31, 33, 45, 52 and 58) - Silgard (quadrivalent HPV vaccine (types 6, 11, 16, 18)
Active Substance(s)	All
Pharmaceutical form(s)	All
Strength(s)	All
Route of administration(s)	All
Marketing Authorisation Holder(s)	GlaxoSmithKline Biologicals S.A. Merck Sharp & Dohme LTD Sanofi Pasteur MSD, SNC

Human papillomavirus (HPV) vaccines have been authorised in Europe for prevention of cervical and various other cancers caused by HPV infection since 2006. Following approval, these vaccines have been introduced in national immunisation programs worldwide, including in most EU member states.

The efficacy and safety of these medicinal products has been clearly demonstrated and the benefit of these vaccines in protecting against HPV related diseases is well established. Since launch, approximately 55 million subjects are estimated to have been vaccinated with Gardasil worldwide. Cumulative marketing exposure to Cervarix is estimated as being around 17 million subjects worldwide.

Routine surveillance of suspected serious adverse drug reaction reports have 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). The vast majority of the reported cases do not have a well-defined diagnosis. These syndromes have been reviewed repeatedly by the PRAC within routine safety follow up procedures, and a relationship with vaccination has not been established in these previous procedures.

For CRPS most common symptoms are severe pain, swelling and changes in the skin temperature and colour of the arms or legs, but may also include amongst other symptoms headache, general fatigue, coldness of the legs, limb pain and weakness. POTS is characterised by an abnormally large increase in heart rate when changing from a lying down to a standing up position, without any orthostatic hypotension. In POTS, this excessive heart rate increase may be accompanied by a range of symptoms which may include light headedness, visual blurring, palpitations, tremulousness and weakness (especially of the legs), as well as fatigue, shortness of breath, chest pain, concentration difficulties, and headaches.

Individual case reports and case series of CRPS and POTS have been reported in the literature following HPV vaccination from several geographically distinct locations. Literature reports of CRPS come from Australia, Germany and Japan and reports of POTS originate from USA, Japan and Denmark.

The Danish Health and Medicines Authority drew the attention of the EMA and the Commission to the issue mentioned above in July 2015. It considers that in view of the seriousness and increasing number of reports and publications raising concern in EU Member States, this safety issue should be evaluated to ensure that sufficient scientific knowledge on the potential relationship is established.

There are uncertainties regarding the underlying pathogenesis for CRPS and POTS and an association between HPV vaccination and CRPS or POTS has also not been established. These conditions have been well known for a long time and before the introduction of the HPV vaccines.

It is recognised that these conditions can occur in the general non-vaccinated population and it is considered important to undertake further review to determine whether the number of cases reported with HPV vaccine is greater than would ordinarily be expected.

The Danish Health and Medicines Authority underlined that the objective with HVP vaccination is to prevent serious life-threatening disease, the exposure of healthy individuals

to the vaccine is extensive, the risk-benefit balance should be favourable and the risks effectively monitored and well characterized.

The persisting uncertainty with regard to causal association between CRPS/POTS and HPV vaccination may have a significant impact on the future confidence in national vaccination programs.

Overall scientific evidence of a potential association between HPV vaccination and the two syndromes should be reviewed and methodologies to further investigate the concerns should be defined, if appropriate.

In view of the above, the European Commission (EC) initiates a procedure under Article 20 of Regulation (EC) No 726/2004 and requests the Agency to assess the above concerns for the centrally authorised medicinal product(s) (mentioned above). The EC requests the Agency to give its opinion as soon as possible and not later than 31 May 2016 on whether there is evidence of a causal association between HPV vaccination and CRPS and/or POTS, and if available information may require updates to the advice to healthcare professionals and patients, including changes to product information or other regulatory measures on the marketing authorisations concerned.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the Committee for Medicinal Products for Human Use on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.

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