09 July 2015
EMA/PRAC/454436/2015

PRAC List of questions

To be addressed by the marketing authorisation holders

Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data

Human papillomavirus (HPV) vaccines

Cervarix: EMEA/H/A20/1421/C/0721/0071

Gardasil: EMEA/H/A20/1421/C/0703/0060

Gardasil 9: EMEA/H/A20/1421/C/3852/0001

Silgard: EMEA/H/A20/1421/C/0732/0054

Marketing authorisation holders: GlaxoSmithKline Biologicals; Merck Sharp & Dohme Limited; Sanofi Pasteur MSD

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1. Background

Human papillomavirus (HPV) vaccines have been authorised in Europe for prevention of cervical and various other cancers caused by HPV infection since 2006. Routine surveillance of suspected serious adverse drug reaction reports of the HPV vaccines have raised questions on the potential association between the use of the vaccines and in particular two syndromes, 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. The need was identified that 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 addition, discussion is needed on whether there is evidence of a causal association between HPV vaccination and CRPS and/or POTS, if research efforts should be strengthened, and if available information may require updates to the advice to healthcare professionals and patients, including changes to product information or other regulatory measures.

In that respect the marketing authorisation holders (MAHs) are requested to respond to the following questions.

2. Questions

Question 1

The MAHs should provide a cumulative review of available data from clinical trials, post-marketing and literature in order to evaluate the cases of CRPS and POTS with their product.

Review and case detection methods should be clearly described and the evaluation should discuss whether the reported cases fulfil published or recognised diagnostic criteria.

Question 2

Please provide an in depth review of cases of CRPS and POTS observed within all clinical studies; with comparison of HPV vaccine groups and control groups. If differences are observed, please discuss potential explanations including risk factors for the development of CRPS and POTS.

Question 3

The MAHs should provide an analysis of the observed number of post-marketing cases of CRPS and POTS in association with their HPV vaccine in comparison to those expected in the target population, stratified by region, if available. The analysis should discuss the assumptions made with respect to the background incidence in the target population and also the influence of potential under-reporting of cases in association with HPV vaccines.

Question 4

The MAHs should provide a critical appraisal of the strength of evidence for a causal association with HPV vaccine for CRPS and POTS. This should consider the available published literature, including epidemiological studies, and also the possible causes and pathophysiology of CRPS and POTS and discuss whether there is biological basis for a possible causal association.

Question 5

The MAHs should discuss the need for possible risk minimisation tools and provide proposals as appropriate.