This English version is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Summary of the Report on the Surveillance Results of HPV Vaccines

December 26, 2013

The Pharmaceuticals and Medical Devices Agency has undertaken an investigation of a possible association between the use of the human papillomavirus (HPV) vaccines and widespread pain.

Non-proprietary Names/ Proprietary Names (Marketing Authorization Holder)

- Recombinant Absorbed Bivalent Human Papillomavirus-like Particle Vaccine/ Cervarix (GlaxoSmithKline K.K.)
- Recombinant Adsorbed Quadrivalent Human Papillomavirus Virus-Like Particle Vaccine/ Gardasil (MSD K.K.)

Adverse Reaction Reports of HPV Vaccines

The PMDA has reviewed 56 cases of adverse reactions reported in Japan as of June 30, 2013 and confirmed that the cases showed different clinical courses and that the pain was not caused by a specific disease after HPV vaccination. It was also noted that the mechanism and pathology of the pain were still unknown in some cases despite thorough clinical tests and treatment in medical facilities. The causal relationship between the HPV vaccines use and widespread pain therefore cannot be ruled out completely in any patient with widespread pain after HPV vaccination because the mechanism and pathology remain unclear.

Published Literature

In overseas studies, autoimmune disorder, neurological disorder and other events may be investigated as possible risks of HPV vaccines. Results of overseas large epidemiologic studies did not suggest that the use of HPV vaccines was associated with increased risk of widespread pain as well as diseases that may cause widespread pain. No regulatory actions have been taken to suspend marketing authorizations for HPV vaccines in other countries. However, some adverse reaction reports and non-clinical studies suggested that HPV vaccines may be associated with increased risks of widespread pain or diseases which may cause widespread pain and that further studies would be warranted. The PMDA is continuing to monitor new information on the issue.

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Conclusion

The PMDA has reviewed all available data including adverse reaction reports, Summaries of Product Characteristics (SmPCs) in the EU and labeling in the U.S., regulatory actions in other countries and published literature on the suspected association between HPV vaccines and widespread pain. The PMDA concluded that the available evidence was insufficient to suspend the marketing authorizations for the HPV vaccines. The PMDA is continuing to review updated clinical data in Japan and will assess the benefit/risk balance when results of further epidemiologic and/or other studies are available both in Japan and other countries. Patients who experienced pain after HPV vaccination should be diagnosed and treated by experts from various specialties for an appropriate differential diagnosis and treatment. The package inserts of HPV vaccines (information to healthcare professionals) have already been revised in June 2013 to address this recommendation. In addition, the Ministry of Health, Labour and Welfare (MHLW) has announced to establish the *Research Project for Treatment Strategies for Chronic Pain*. It is important to thoroughly review any cases of widespread pain after HPV vaccination, especially cases that described diagnosis or treatments by experts from various specialties, in order to decide whether further regulatory action should be taken. The PMDA is planning to review not only risk information of HPV vaccines but also cases in which the pain was relieved or resolved.

The Marketing Authorization Holders (MAHs) of HPV vaccines are required to gather more data on the risks of HPV in a timely manner in order to judge the necessity of additional studies and/or safety measures. The MAHs should provide updated information to healthcare professionals, patients and their caregivers as it becomes available.

Note: This document is available on the PMDA's website (http://www.pmda.go.jp/english/index.html).

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