Pharmaceuticals and Medical Devices Agency

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.

Main information on the safety review meeting on Cervarix and GARDASIL

- Non-proprietary name: Recombinant adsorbed bivalent human papillomavirus-like particle vaccine (derived from Trichoplusia ni cells)
  Brand name: Cervarix
- Non-proprietary name: Recombinant adsorbed quadrivalent human papillomavirus virus-like particle vaccine (Yeast Origin)
  Brand name: GARDASIL

The followings are main information on the safety review meeting on Cervarix and GARDASIL.

In the safety review meeting, the members including expert advisers reviewed 5 suspected cases of complex regional pain syndrome (2 cases were related to Cervarix, 3 cases were related to GARDASIL, those cases had been reported by April 30, 2013) and 34 cases* of extensive pain (32 cases were related to Cervarix, 2 cases were related to GARDASIL, those cases had been reported by March 31, 2013). As a result of the examination, members determined that there is a need to alert people that persistent pain which is not localized at the injection site, numbness, weakness, etc., may occur after vaccination, even though the mechanisms of pathogenesis are unclear.

As a result of the safety review, various pathological conditions were observed and clinical courses were different depending on each case. While the mechanisms of pathogenesis and a causal relationship between the vaccines and the adverse reactions are unclear, some symptoms occurred shortly after the vaccination. Some patients developed symptoms of neurological or immunological diseases after vaccination. Although there is currently insufficient evidence of a causal association with the human papillomavirus (HPV) vaccines, the possibility of neurological or immunological diseases associated with the vaccination cannot be ruled out. For these reasons, the members concluded that it is necessary to provide information that persistent pain which is not localized at the injection site, numbness, weakness, etc., may occur and

that vaccine recipients and their guardians should be instructed to consult a healthcare provider who can provide appropriate medical care including making neurological and immunological differential diagnosis, if any abnormalities are observed after vaccination.

*Of the adverse reaction reports related to pain, the following cases were excluded:
1) cases where the pain is associated with syncope and anaphylaxis, 2) cases of mild local pain, 3) cases where causative diseases were recognized, 4) cases of head ache or muscle pain associated with fever, and the patients recovered within days, 5) cases of spasm, arrhythmia, etc., without pain, 6) cases where the pain is localized at the injection site on the upper arm , 7) cases where the patients' chief complaints were any symptoms other than pain (head ache, etc.)

Related Information:

Japanese version of the safety review report:

http://www.info.pmda.go.jp/kaitei/file/20130614frepno1.pdf

<Recommended change on the Important Precautions section of the package insert of the vaccines>

Current statement	Recommended change on the package insert
2. Important Precautions Omission	2. Important Precautions Omission “Although the mechanisms of pathogenesis are unclear, severe pain which is not localized at the injection site (e.g. muscle pain, arthralgia and skin pain, etc.), numbness, weakness, etc., may occur after vaccination and these symptoms may persist for long time. Vaccine recipients and their guardians should be instructed to consult a healthcare provider who can provide appropriate medical care including making neurological and immunological differential diagnosis if any abnormalities are observed after vaccination.”