EMA/226536/2015

Summary of the risk management plan (RMP) for Gardasil 9 (human papillomavirus 9-valent vaccine (recombinant, adsorbed))

This is a summary of the risk management plan (RMP) for Gardasil 9, which details the measures to be taken in order to ensure that Gardasil 9 is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Gardasil 9, which can be found on Gardasil 9's EPAR page.

Overview of disease epidemiology

Gardasil 9 is a vaccine used in males and females above 9 years of age to prevent certain cancers and pre-cancerous conditions (abnormalities that can lead to cancer) caused by human papillomavirus (HPV) infection. HPV infection is the most common sexually transmitted disease worldwide. Over 50% of sexually active adults become infected with HPV during their lifetime. The highest rates of HPV infection occur soon after people become sexually active. The risk of an HPV infection increases with the number of sexual partners during an individual's lifetime. Of the many different types of human papillomavirus, some are harmless and others can cause diseases of the genital areas. While in most cases the virus is eliminated naturally, if it persists it can cause genital warts, pre-cancerous conditions or cancer.

Gardasil 9 is indicated for active immunisation against:

- Pre-cancerous conditions and cancers affecting the cervix, vulva, vagina and anus caused by vaccine HPV types.
- Genital warts (condyloma acuminata) caused by specific HPV types.

Cervical cancer

Cervical cancer develops in the cervix (the lower part of the womb) and may result from infection with HPV, generally transmitted during sexual activity. It is a common type of cancer in women, affecting about 530,000 women worldwide and causing 275,000 deaths each year. It usually affects women aged 35 to 55 years.

Vaccination against HPV and regular screening (Pap smear tests) for early signs of pre-cancerous conditions can prevent cervical cancer.

Vulvar cancer

Vulvar cancer is a cancer that develops in the external female genital organs (vulva). Vulvar cancer may result from infection with HPV, transmitted during sexual intercourse. There are no routine screening tests for this cancer.

Vaginal cancer

Cancer of the vagina is a cancer of the birth canal; it is uncommon. Vaginal cancer may result from infection with HPV, transmitted during sexual intercourse. There are no routine screening tests for this cancer.

Genital warts

Genital warts (condylomata acuminata) are generally benign growths in or around the vagina, penis, or rectum caused by sexually transmitted HPV. Genital warts grow rapidly and sometimes cause burning pain.

Anal cancer

Anal cancer is a rare type of cancer that affects the very end of the large bowel (large intestine) and that may result from infection with HPV.

Summary of treatment benefits

Gardasil 9 can provide protection against infection by nine types of HPV (types 6, 11, 16, 18, 31, 33, 45, 52 and 58), as seen in four main studies.

The first study looked at the effectiveness of Gardasil 9 in over 14,000 women aged between 16 and 26 years. The study looked at how many women given Gardasil 9 developed disease (growths or cancer) due to HPV infection caused by HPV types 31, 33, 45, 52 and 58 when compared with Gardasil vaccine (a previously approved vaccine which protects against types 6, 11, 16 and 18). This study showed that 1 out of 6,016 women vaccinated with 3 doses of Gardasil 9 developed disease related to HPV types 31, 33, 45, 52 and 58, compared with 30 out of 6,017 women vaccinated with 3 doses of Gardasil. This study also showed that antibody levels against types 6, 11, 16 and 18 were adequate to protect against these four types of HPV infection. The women were followed up for around three and a half years after the third dose of the vaccine.

The second study in 3066 subjects compared the effect of Gardasil 9 in girls and boys aged nine to 15 years with the effect of Gardasil 9 in young women aged 16 to 26 years. The main measure of effectiveness was the development of antibodies against HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 one month after the third dose. The study showed that the vaccine stimulates the production of adequate levels of antibodies against HPV of all nine types in girls and boys aged between nine and 15 years when compared with women 16-26 years of age, for whom protection against disease was demonstrated in the first study.

The third study compared the effect of Gardasil 9 with the effect of Gardasil in 600 girls aged 9 to 15 years. The study looked at the development of antibodies one month after the third dose, and it showed that girls vaccinated with Gardasil 9 have similar levels of protection against types 6, 11, 16 and 18 as girls vaccinated with Gardasil.

The fourth main study compared the levels of antibodies against all nine HPV types one month after the third dose in around 1,419 young men aged 16 to 26 with those in 1,101 women aged 16 to 26. This study found that Gardasil 9 stimulates similar levels of protection against all nine virus types in young men and women.

Unknowns relating to treatment benefits

The long-term antibody response and the period that Gardasil 9 prevents HPV disease after vaccination are not yet known. In addition, the following groups were not studied in clinical trials, so it is not known if Gardasil 9 prevents HPV disease in these individuals:

- Individuals younger than 9 years of age or older than 26 years of age;
- Individuals with medical conditions that could affect the vaccine's safety, immunogenicity and/or how well the vaccine works;
- Pregnant women.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Immediate hypersensitivity (sudden allergic reaction) Sudden signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing.	As with any medicine or vaccine, severe allergic reactions may occur with this vaccine. Allergic reactions may be serious and require immediate treatment. Allergic reactions usually develop very quickly after the injection. In clinical studies of Gardasil 9, most of the cases of hives (urticaria) were mild to moderate in intensity and reported as resolved.	Individuals with a history of an allergic reaction to Gardasil or Silgard (an identical vaccine to Gardasil) are at increased risk of an allergic reaction to Gardasil 9. These individuals should not receive Gardasil 9, as indicated in the product information. In addition, individuals who develop symptoms of an allergic reaction after a dose of Gardasil 9 vaccine should not receive further doses.

Important potential risks

Risk	What is known
Product confusion between Gardasil and Gardasil 9	There is the potential for confusing Gardasil 9 with the Gardasil vaccine. No safety issue in the case of product confusion has been identified. However, since Gardasil 9 protects against five more types of HPV viruses than Gardasil, the full benefit of Gardasil 9 vaccine in the prevention of disease related to the additional HPV types contained in the vaccine may be missed.
Mixed regimen between Gardasil/Silgard and	Because there is more than one type of vaccine against HPV on the market, patients could receive a vaccination course involving more than one HPV vaccine type (a mixed regimen). The effects of such a mixed regimen have not

Risk	What is known
Gardasil 9 (where more than one type of vaccine is given in the same course)	been studied and if this happens, patients might not be fully protected against the additional HPV types included in Gardasil 9. It is recommended that patients who receive a first dose of Gardasil 9 complete the 3-dose vaccination course with Gardasil 9 vaccine.

Missing information

Risk	What is known
Exposure during pregnancy	Gardasil 9 has not been systematically studied in pregnant women, but data involving more than 1,000 cases where women were inadvertently given the vaccine while pregnant did not indicate any birth defect or harm to the newborn child. However, this evidence is not enough to recommend use during pregnancy and vaccination should be postponed until pregnancy is over.
Viral type replacement	Viral type replacement occurs when, by blocking infection with certain HPV types, use of the vaccine could result in increase of disease caused by other types of HPV infection. To date, there are no data to suggest that Gardasil 9 vaccine will cause viral type replacement.
Long-term effectiveness and immunogenicity	Gardasil 9 prevents HPV disease in most people for at least 4 years after receiving all 3 doses of vaccine. In studies with Gardasil/Silgard, the vaccine was shown to prevent HPV disease for at least 6 years following vaccination. It is expected that Gardasil 9 vaccine will also provide long-term protection. The duration of protection of Gardasil 9 vaccine against HPV disease beyond 4 years after receipt of the full 3-dose vaccination course has not yet been evaluated. However, a set of subjects participating in the Gardasil 9 vaccine clinical program will be followed for more than 10 years in order to evaluate long-term protection against HPV disease.
Immunogenicity and safety in subjects above 26 years of age	Even though Gardasil 9 has not been evaluated in subjects over 26 years of age, Gardasil 9 effectiveness can be extrapolated to this population based on the following considerations: The Gardasil/Silgard vaccine clinical development program has demonstrated that the Gardasil/Silgard vaccine is efficacious in preventing HPV diseases for both females 16 to 26 years of age and females 24 to 45 years of age. The totality of results from the Gardasil 9 vaccine immunogenicity studies support that Gardasil 9 and Gardasil have similar immunogenicity profiles. Therefore, it is anticipated that this would also apply to female subjects 27 to 45 years of age. However, a post-marketing study of the Gardasil 9 vaccine in women 27 to 45 years of age will be conducted to confirm this assumption.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Gardasil 9 can be found on Gardasil 9's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Pregnancy registry	To monitor pregnancy outcomes in women exposed to Gardasil 9 vaccine during pregnancy.	Inadvertent exposure to vaccine during pregnancy.	Planned	**Interim Reports:** 31-Aug-2016 31-Aug-2017 31-Aug-2018 31-Aug-2019 31-Aug-2020 **Final Report:** Expected 18 months after enrollment of the last patient.
V503-021 Nordic Long-term Follow-Up Study (10-Year extension in subjects from V503-001)	To monitor the long term effectiveness and immunogenicity of Gardasil 9.	- Viral type replacement. - Long-term effectiveness/ immunogenicity.	Planned	**Interim Reports:** Expected 4Q2017 Expected 4Q2019 Expected 4Q2021 Expected 4Q2023 **Final Report:** Expected 31-Dec-2026
V503-002-20 Postdose 3 Follow-Up Study (10-Year Postdose 3 Extension)	To monitor the long-term effectiveness and immunogenicity of Gardasil 9.	Long-term effectiveness/ immunogenicity.	Planned	**Interim 72-Month Report:** Expected 4Q2017 **Interim 96 Month Report:** Expected 4Q2019 **Final Report:** Expected 31-Mar-2023
A post-marketing immunogenicity and	- To demonstrate immunogenicity for	Immunogenicity and safety in females	Planned	**Final Report:** Expected 1Q 2019

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
safety study of the 9vHPV vaccine in women 27 to 45 years of age	Gardasil 9 in women 27 to 45 years of age. - To collect data on the safety profile of Gardasil 9 in women 27 to 45 years of age.	greater than 26 years of age.		

Studies which are a condition of the marketing authorisation

None.

Summary of changes to the risk management plan over time

Major changes to the Risk Management Plan over time

Not applicable.

This summary was last updated in 05-2015.