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To the Minister of Health, Welfare and Sport
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2024035965

Date 8 October 2024
Re: GVS advice 9 valent human papilloma virus (9vHPV) vaccine (Gardasil®) for the prevention of HPV-related premalignant lesions and carcinomas in a medical high-risk group

National Health Care Institute

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Medicinal Products
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Our reference
2024035965

Dear Ms Agema,

In the letter dated 25 March 2024 [CIGB 24-06770], your predecessor asked the National Health Care Institute for a substantive review of the inclusion of the 9vHPV vaccine (Gardasil®) for active immunisation against HPV-related premalignant lesions and carcinomas (cervix, vulva, vagina and anus) in women following treatment of precursors of cervical carcinoma in List 1B of the Medicine Reimbursement System (GVS).

The National Health Care Institute, advised by the Scientific Advisory Board (WAR), has now completed this assessment.

Infection with HPV (human papilloma virus) is caused by sexual contact. In some cases, the body does not clear the virus and persistent infection can cause cervical cancer. The incidence and prevalence of cervical cancer in 2022 were 957 and 3537, respectively. After 5 years, approximately 74% are still alive (RIVM figures of 2022). The HPV infection can also play a role in the development of other cancers, such as cancer of the anus, penis, vagina, labia, oral cavity and throat. In addition, HPV can cause genital warts. Vaccination of 13-year-olds to prevent these conditions due to an HPV infection is part of the National Immunisation Programme.

Specific reimbursement is now being requested for immunisation with the 9vHPV vaccine for unvaccinated women who have been diagnosed with early-stage cervical cancer on a smear test and who are being treated surgically for this purpose. According to the product information, the 9vHPV vaccine is for prophylactic use only and has no effect on active HPV infections or pre-existing clinical disease caused by HPV. Results from previous prevention studies cannot be extrapolated to this high-risk group of women, as they are already infected with HPV at the time of vaccination and had precursors of cervical carcinoma.

There are many different types of this virus. The vaccine from this review recognises 9 types of virus, hence '9 valent'.

Registered indication: 9vHPV vaccine (Gardasil®) is indicated for active immunisation of individuals from the age of 9 years against the following HPV

diseases: Premalignant lesions and cancers affecting the cervix, vulva, vagina and anus caused by HPV types that are counteracted by this vaccine, and genital warts (Condyloma acuminata) caused by specific HPV types.

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It is available as an injection suspension in a pre-filled syringe (0.5 ml).

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Claim by the marketing authorisation holder: 9vHPV vaccine for active immunisation against HPV-related premalignant lesions and carcinomas of the cervix, vulva, vagina and anus has an added value compared to no vaccination in women following treatment of precursors of cervical carcinoma.

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Advice

The National Health Care Institute advises you to not include the 9vHPV vaccine for active immunisation against HPV-related premalignant lesions and carcinomas of the cervix, vulva, vagina and anus in women after treatment of precursors of cervical carcinoma in the GVS.

The considerations for this advice are explained below.

Substantive assessment

Therapeutic value:

The effectiveness and safety of HPV vaccination with 4vHPV vaccine for this indication has been studied in two randomised studies compared to no vaccination. The 9vHPV vaccine is an extension of the 4vHPV vaccine and recognises 5 additional HPV subtypes. The results of these studies suggest that HPV vaccination may have an effect on the rate of recurrence of precursors of cervical cancer. Whether this effect is also clinically relevant is uncertain because the confidence interval crosses the limit of clinical relevance ($RR < 0.5$) set by the professional group. In addition, a large proportion of women (25%) discontinued the study after randomisation. More than double the number of women in the non-vaccination group left the study, compared to the vaccination group. This may have been affected by the study not being blinded. This introduces so much uncertainty that, on the basis of these two studies, it is not possible to speak with sufficient confidence of a clinically relevant effect. Two overarching analyses of HPV vaccination studies, including the above studies, in this group of women show similar uncertainty around the scope of the effectiveness. The researchers therefore concluded that the effect was moderate to very low and that more high-quality research should be carried out. This supports the findings of the National Health Care Institute.

There is no evidence that HPV vaccination results in more severe intervention-related adverse effects or more patients who discontinued treatment compared to no vaccination.

To summarise, based on a GRADE assessment, the evidence presented is of insufficient quality to demonstrate an added value compared to no vaccination. With those results, the 9vHPV vaccine does not meet the 'established medical science and medical practice'.

In the future, an ongoing study with 9vHPV vaccine might generate data with a higher evidence quality that could lead to a different conclusion.

Should you need any further information, please do not hesitate to contact us. The assessment report has been added as an annex (pharmacotherapeutic report).

Yours sincerely,

Mark Janssen
Chairperson of the Executive Board

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