REPUBLIC OF BULGARIA
NATIONAL COUNCIL ON PRICES AND REIMBURSEMENT OF MEDICINAL PRODUCTS

HEALTH ASSESMENT TECHNOLOGY

Gardasil 9

0.5 ml suspension for injection in pre-filled syringe

1 pre-filled syringe + 2 needles

INN Papilloma virus (human types 6, 11, 16, 18, 31, 33, 45, 52, 58)

Therapeutic indication(s)	Gardasil 9 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 vaccine HPV types • Genital warts (*Condyloma acuminata*) caused by specific HPV types.
Start/end date of procedure	25.10.2022 – 01.06.2023
Final decision	Inclusion in Annex 3 Medicinal products intended for the treatment of AIDS, or infectious diseases, or diseases beyond the scope of the Health Insurance Act, which ae reimbursed according to the procedure established in Item 8 of Article 82, paragraph 1 of the Health Act, as well as vaccines for compulsory immunisations and boosters, vaccines on special indications and in an emergency, specific sera, immunoglobulins, designated by the ordinance referred to in Article 58, paragraph 2 of the Health Act.

Summary of the report on the clinical and pharmacoeconomic assessment of the health technology of the medicinal product Gardasil 9

Health problem

Human papillomavirus (HPV) infection is the most common sexually transmitted infection. HPV represents a large group of double-stranded, non-enveloped, epithelial-tropic DNA viruses from the Papillomaviridae family. By the age of 45, 80% of women and men will have contracted HPV. Although most HPV infections resolve without consequences and spontaneously clear within a few years, persistent HPV infection poses a public health problem as it is associated with cervical cancer (CC), as well as cancers of the anus, vagina, vulva, penis, and some forms of skin and oropharyngeal cancer.

Infections with high-risk HPV usually do not cause symptoms. Precancerous changes in the cells caused by persistent HPV infection of the cervix rarely cause symptoms, making regular cervical cancer screening important. Precancerous changes in other body parts can cause symptoms such as itching or bleeding. If HPV infection develops into cancer, it can cause symptoms such as bleeding, pain, or glandular swelling. Benign skin lesions associated with HPV include common warts (verruca vulgaris), plantar warts, and flat warts. The most common HPV types found in benign skin lesions are HPV types 1 to 4. Malignant skin tumors associated with HPV include cutaneous squamous cell carcinoma and basal cell carcinoma. HPV infection is also associated with benign and malignant lesions of the oral mucosa, respiratory tract, esophagus, and eyes. HPV types 6 and 11 are often found in benign lesions, while HPV types 16 and 18 are frequently found in cancers.

Molecular screening tests for high-risk HPV subtypes and screening for precancerous epithelial lesions play an important role in HPV control as a second line of defense. Given that HPV is associated with the greatest medical economic burden among patients with cervical cancer, there are currently several screening programs aimed at preventing the development of this oncological disease.

Gardasil 9 is an adjuvanted, non-infectious, recombinant, 9-valent vaccine. It is made from highly purified virus-like particles (VLPs) of the major capsid L1 protein of four HPV types (6, 11, 16, 18), the same as in the qHPV vaccine, and five additional HPV types (31, 33, 45, 52, 58). It contains the same amorphous aluminum hydroxyphosphate sulfate adjuvant as the qHPV vaccine. VLPs cannot infect cells, replicate, or cause disease. The efficacy of the L1 VLP vaccines is believed to be mediated by the development of a humoral immune response. The HPV genotypes included in the vaccine, HPV 6, 11, 16, 18, 31, 33, 45, 52, 58, will be referred to as vaccine HPV types.

Efficacy data

The therapeutic efficacy and safety profile of Papilloma virus (human types 6, 11, 16, 18, 31, 33, 45, 52, 58) have been analyzed in three efficacy clinical trials: **V503-001 (NCT00543543), V503-001-04 (NCT00543543), and V503-021 (NCT02653118)**, as well as in five immunomodulation trials for adolescents: **V503-002 (NCT00943722), V503-002-10, V503-002-20, V503-010 (NCT01984697)**, and **V503-009 (NCT01304498)**. Additionally, three trials focused on concomitant administration: **V503-005 (NCT00988884), V503-007 (NCT01073293), and V503-006 (NCT01047345).**

- **Clinical Trial V503-001 (NCT00543543)** is a Phase 2/3, double-blind, randomized, controlled trial with dose variation.
- **Clinical Trial V503-001-04 (NCT00543543)** is an extension trial with a single arm of V503-001.
- **Clinical Trial V503-021 (NCT02653118)** is a registry-based extension of V503-001 for long-term follow-up; currently ongoing.
- **Clinical Trial V503-002 (NCT00943722)** is a Phase III, open-label, randomized clinical trial. V503-002 has two extensions: the open-label V503-002-10 with a single arm for assessing antibody persistence up to month 36 (girls and boys who received Gardasil 9 in V503-002) and the open-label V503-002-20 with a single arm for evaluating long-term immunogenicity, efficacy, and safety over 10 years after the third dose (girls and boys who received 3 doses of Gardasil 9 in V503-002). Clinical trials V503-002-10 and V503-002-20 are open-label, single-arm extensions of V503-002.
- **Clinical Trial V503-010 (NCT01984697)** is a randomized open-label trial lasting 37 months.
- **Clinical Trial V503-009 (NCT01304498)** is a multicenter, double-blind, randomized clinical trial. Participants were randomized (1:1) to receive Gardasil 9 or Gardasil on Day 1, Month 2, and Month 6.
- **Clinical Trial V503-005 (NCT00988884)** is a multicenter, open-label, randomized comparative trial. Participants were randomized (1:1) to a group receiving the vaccines concomitantly or separately.
- **Clinical Trial V503-007 (NCT01073293)** is a multicenter, open-label, randomized trial. Participants were randomized (1:1) to receive a 0.5 mL dose of Gardasil 9 intramuscularly on Day 1, Month 2, and Month 6 and a 0.5 mL dose of Repevax on Day 1 (concomitant group, n = 526) or Month 1 (separate group, n = 528).
- **Clinical Trial V503-006 (NCT01047345)** is a randomized, double-blind trial. Participants were randomized approximately 2:1 to receive Gardasil 9 or placebo. The vaccine or placebo was administered as a series of intramuscular injections (0.5 ml) on Day 1, Month 2, and Month 6.

Results show that immune responses for Gardasil 9, measured by geometric mean titer (GMT), are not less than those for Gardasil, with the mean (Gardasil 9) GMT ratios for anti-HPV 11 GMT in

16 to 26-year-old women being 0.80. Based on these data, the efficacy results for Gardasil related to HPV 6, 11, 16, and 18 can be extrapolated to girls aged 9 to 15 and young women aged 16 to 26 receiving the 3-dose regimen with Gardasil 9. In the V503-001 trial, pronounced antibody responses to HPV types 6, 11, 16, and 18 were observed at Month 3 (1 month after the second dose) and Month 7 (1 month after the third dose); cLIA GMTs decreased over time from Month 7 to Month 36 and then plateaued. Anti-HPV 6, 11, 16, and 18 cLIA GMTs at Month 7 were not lower in the Gardasil 9 group compared to the Gardasil group (the lower bound of the 95% CI of the GMT ratio [Gardasil 9] is above 0.67). GMT ratios (Gardasil 9) and associated 95% CIs varied slightly over time: from Month 7 to Month 42, GMT ratios ranged from 1.02 to 1.03 for HPV 6, 0.80 to 0.83 for HPV 11, 0.96 to 1.02 for HPV 16, and 1.17 to 1.26 for HPV 18, indicating consistency of immune responses over time. The final analysis of the V503-001 trial shows 96 to 97% efficacy regarding primary and secondary endpoints. Gardasil 9 prevents 97% of HPV 31/33/45/52/58-related 12-month persistent infections, 97% of high-grade cervical disease (including 100% of HPV 31/33/45/52/58-related CIN 3), 90 to 98% of cervical cytological abnormalities, and cervical procedures (biopsy, definitive therapy). The efficacy results are similar to those reported after the initial analysis, demonstrating that vaccine efficacy is maintained throughout the trial, up to 6 years after the first dose. In the V503-002 trial, the differences between GMTs in girls and GMTs in young women range from 1.83 to 2.62 times. Differences between GMTs in boys and GMTs in young women range from 2.10 to 3.33 times. The lower bound of the 95% CI for GMT ratios ranges from 1.63 to 2.27 for girls and from 1.88 to 2.89 for boys; the predefined non-inferiority criterion was met for all comparisons. In the V503-010 clinical trial, 1 month after the third dose, the seroconversion rate to the 9 vaccine-related HPV types in girls and boys aged 9 to 14 years ranged from 97.9% to 100%. The predefined non-inferiority criterion was met for all comparisons.

Safety data

The most common adverse drug reactions are headache, pain swelling, and erythema at the injection site.

Data on comparators

The comparative alternatives chosen are Gardaxil 4 and Cervarix.

Pharmacoeconomic indicators

Published health technology assessments performed by governmental institutions intended for the health care systems of other countries

One assessment from another governmental institution, Haute Autorité de santé (HAS) in France, has been published. The decision supports the vaccination of boys and girls to prevent human papillomavirus (HPV) infection and genital warts, in accordance with the proposed vaccination schedule.

Applied analysis
A cost-utility analysis (CUA) has been applied, where the final outcome regarding health benefits is represented as quality-adjusted life years (QALY). The comparative alternative chosen is passive behavior, i.e., not vaccinating, and is compared against the screening program for primary prevention of HPV diseases. The perspective is that of the National Health Insurance Fund (NHIF) and the Ministry of Health (MoH). The time horizon is 100 years, though a more realistic period would be 40 years. The discount rate is 3.5% annually. A population-based dynamic transmission model was developed to evaluate the cost-effectiveness of Gardasil 9, assessing protection against HPV types 6, 11, 16, 31, 33, 45, 52, and 58, covering both direct and indirect (i.e., collective) protective effects of vaccination.

At a favorable cost-effectiveness threshold of 51,897 BGN/QALY (3 times GDP per capita according to NSI data for 2020), the incremental cost-effectiveness ratios (ICER) determine Gardasil 9 vaccination as a cost-effective strategy compared to screening for preventing the following HPV-related diseases: cervical cancer, vaginal cancer, vulvar cancer, genital warts, anal cancer, head/neck cancer, and penile cancer.

Costs for the assessed health technology
The costs of vaccination and the vaccine itself are included. For the comparative alternative, costs associated with screening, treatment of affected individuals, and diagnostic tests are included. Costs for men are also assessed, although it is noted that the vaccine is evaluated for use in women only. Additionally, only costs related to pharmacotherapy are included, not those related to surgical treatment. The costs for screening include only those related to medical consultations and Pap smears, not population screening.

Subgroup analysis
No subgroup analyses have been applied.

Budget impact analysis
The budget impact analysis is conducted from the perspective of the paying institutions – the NHIF and MoH. The time horizon is 5 years. The target population includes girls aged 10 to 13 years who are eligible for vaccination against the following HPV-related diseases:

- Premalignant lesions and cancers affecting the cervix, vulva, vagina, and anus caused by vaccine HPV types;
- Genital warts (Condyloma acuminata) caused by specific HPV types.

The projected number of patients aged 10-11 years receiving the first dose in the first year is 13,477, and 13,822 in the fifth year. The projected number of patients aged 10-11 years receiving the second dose in the first year is 0, and 8,790 in the fifth year. The projected number of patients aged 12-13 years receiving the first dose in the first year is 4,789, and 4,911 in the fifth year. The projected number of patients aged 12-13 years receiving the second dose in the first year is 0, and 3,953 in the fifth year.

The analysis forecasts an increase in costs for the NHIF and MoH over a five-year period, without accounting for risk-sharing agreements and patient access schemes.

Conclusion

Primary prevention of HPV infection with high-risk cancerous HPV types is the most effective method for reducing morbidity and mortality from HPV-related cancers. The health technology Gardasil 9 aims to prevent HPV infection and reduce cancer incidence associated with HPV. The increase in costs for the NHIF and MoH over a five-year period would be justified given the additional health benefits.