WHO PUBLIC ASSESSMENT REPORT (WHOPAR)			
Cecolin® Recombinant Human Papillomavirus Bivalent (Types 16, 18) Vaccine			
Xiamen Innovax Biotech Co., Ltd., China			
Ref. no. PQ-FVP-2020-452-389-WHOPAR-01			
Effective date: 10 July 2024	**Published: 14 August 2024**	**Last Update: 17 January 2025**	**Version: 4**

What is Cecolin®?

Cecolin® is a suspension for injection of Recombinant Human Papillomavirus Bivalent (Types 16, 18) vaccine presented in a single dose glass vial. The vaccine is adjuvanted and upon storage, a fine white deposit with a clear colourless supernatant can be observed. Would be a suspension ready to use after thorough agitation.

Each dose of vaccine (0.5 mL) contains:

Active components and quantity per dose	
Recombinant human papillomavirus type16 L1 protein	40 μg
Recombinant human papillomavirus type18 L1 protein	20 μg
Excipients	
Aluminium hydroxide (Chinese Ph., Eur. Ph.) as adjuvant	
The formulation system is complemented by excipients like sodium chloride (Chinese Ph., Eur. Ph., USP), polysorbate 80 (Chinese Ph., Eur. Ph., USP), sodium dihydrogen phosphate-dihydrate (Chinese Ph., Eur. Ph., USP), disodium hydrogen phosphate dihydrate (Chinese Ph., Eur Ph., USP) and water for injection (Chinese Ph., Eur. Ph., USP) q.s.	

Cecolin® comes in a pack of 10 vials. Each vaccine vial consists of 1 dose of 0.5 mL of vaccine. The vaccine should be administered by intramuscular injection only, preferably in the deltoid muscle of upper arm.

Cecolin® is filled in a Type 1 made of neutral borosilicate glass vial. The vials closure system is complemented with a stopper made of butyl, bromobutyl, with aluminium flip-off seal and plastic cap.

The stability data submitted by the prequalification holder supports a shelf life of 36 months when the vaccine is stored between 2°C to 8°C. The vaccine should be shipped and stored at this recommended temperature, and it should not be frozen. The data provided support the use of a Vaccine Vial Monitor (VVM) Type 14 and, if required, it will be part of the vaccine label.

Cecolin® is manufactured at a Xiamen Innovax Biotech Co., Ltd. at No. 52, Shanbianhong East Road, Haicang District, Xiamen City, Fujian Province, China.

What is Cecolin® used for?

Cecolin® is indicated for women aged 9 to 45 years against cervical cancer disease caused by oncogenic human papilloma virus (HPV) types 16 and 18, as recommended by WHO (WHO position paper, December 2022. Weekly Epidemiological Record No 50, 2022, 97, 645–672.).

Cecolin® is used for preventing the following diseases caused by oncogenic human papillomavirus (HPV) types 16 and/or 18:

1. Cervical cancer.
2. Cervical intraepithelial neoplasia Grade 2 or 3 (CIN2/3) and adenocarcinoma in-situ (AIS).
3. Cervical intraepithelial neoplasia Grade 1 (CIN1).\
4. Persistent infections of HPV types 16 and/or 18.

How is Cecolin® used?

Cecolin® should be administered in 3 doses of 0.5mL each, by intramuscular injection, according to the schedule of 0, 1, and 6 months.

Primary vaccination

- Female from 9 to 14 years of age: Two doses of 0.5 mL or three doses of 0.5mL.
- Female from 15 years and above: Three doses of 0.5 mL, at 0,1 and 6 months.

If flexibility in the vaccination schedule is necessary, then:

- For 2-dose schedule, the second dose should be administered at least 5 months after the first dose.
- For 3-dose schedule, the second dose should be administered within 1 – 2 months after the first dose, and the third dose can be injected within 5 – 8 months after the first dose.

Booster Vaccination

- At present, is has not been determined whether the booster vaccination is required for Cecolin®.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Cecolin® should not be used in individuals who develop symptoms of hypersensitivity after receiving a dose of Cecolin®

What are the vaccine characteristics?

Cecolin® must be stored as recommended by manufacturer, between 2°C to 8°C. Under these recommended storage conditions, the vaccine is stable for 36 months from the date of manufacture. Upon storage, a fine white deposit with a clear colourless supernatant can be observed.

The vaccine does not contain preservative.

Cold chain volume per dose is 14.29 cm^3/dose in the primary carton of 10 vials.

Who is the regulatory authority responsible for its oversight vis a vis WHO?

National Medical Products Administration (NMPA) of the People's Republic of China (PRC) is the Regulatory Authority of record for the WHO prequalification procedure. The Marketing Authorization (MA) for Cecolin® was issued by the NMPA on 30 December 2019.

How has Cecolin® been studied from the clinical point of view?

The clinical development program of the HPV16/18 vaccine was based on four clinical trials.

A **Phase I** open-label uncontrolled study in 38 women 18-55 years of age (yoa) to assess reactogenicity and safety of the HPV16/18 bivalent vaccine at the 90 μg (60 μg of HPV16 / 30 μg of HPV18) dose level over a 7-month observation period (each dosing formulation of the HPV16/18 bivalent vaccine has 2-fold higher content of type 16 VLP relative to type 18 VLP).

A **Phase II** randomized, double-blind controlled, dose-finding study in 1600 women 18-25 years of age to assess safety and immunogenicity of three dose levels of the HPV16/18 bivalent vaccine , *i.e.* 30 μg (20 μg of HPV 16 and 10 μg of HPV 18), 60 μg (40 μg of HPV 16 and 20 μg of HPV 18), and 90 μg (60 μg of HPV 16 and 30 μg of HPV 18) over a 7-month observation period and select the dose for subsequent studies.

A **Phase III** randomized, double-blind, controlled study in 7372 women 18-45 years of age to assess safety, efficacy and immunogenicity of the HPV 16/18 vaccine at 60 μg (40 μg of HPV 16 and 20 μg of HPV 18) over a ~66-month observation period (median: 68.7 months), with an interim analysis triggered by a predefined number of primary efficacy endpoint events. The observation period for the interim analyses was approximately 42 months (median: 42.5 months). The two sets of analyses are referred to as 42m interim analysis and 66m final analysis. Three manufacturing lots of the HPV16/18 bivalent vaccine were included in the study and compared to demonstrate consistency of immune response across batches.

A partially randomized, controlled **Bridging study** in 979 girls and women 9 to 26 year of age to assess reactogenicity and safety and demonstrate immunological non-inferiority of: HPV 16/18 0/1/6m in girls 9 to 17 y to HPV16/18 0/1/6m in women 18-26 year of age, HPV16/18 0/6m in girls 9 to 14 year of age to HPV16/18 0/1/6m in women 18-26 year of age.

The vaccine was safe and showed a good immunogenicity.

In **Phase III study -Primary Efficacy**:

1. *High-grade precancerous lesions,* incidence of CIN2+ and/or VIN2+ and/or VaIN2+ -the vaccine had 100% (95% CI: 55.7% to 100.0%) efficacy. For HPV 16 and/or HPV18 and for HPV 16 alone, the statistical success criterion was met. There was only one case associated with HPV 18 and no statistically based conclusion can be drawn.

2. *Persistent infection:* Vaccine efficacy was 96.4% (95% CI: 78.4% to 99.9%) for HPV16 and 100% (95% CI: 74.4% to 100 %) for HPV18, both meeting the pre-defined success criterion and both statistically significant ($p<0.001$).

The secondary endpoints for HPV16 and/or HPV18-related precancerous/cancerous lesions and infections were all significantly in favour of the Innovax HPV16/18 vaccine, with vaccine efficacy consistently above 90%, except for cases in which DNA test of the corresponding type was newly found positive at the visits after baseline (transient (non-persistent) infection). Protection rate for the transient (non-persistent and persistent) HPV 16 and/or HPV 18 infections was 68.5% (95% CI: 55.5% - 78.1%) ($P<0.001$).

The assessment conducted on the safety and tolerability of Innovax HPV vaccine was found acceptable.

Other information about evaluation of Cecolin®

Evaluation of Cecolin® prequalification application was based on the review of the information submitted to WHO by Xiamen Innovax Biotech Co., Limited, (PRC), the WHO outcome of the site inspection to the facility where the vaccine is manufactured and the satisfactory results of the test of vaccine samples in WHO contract laboratories.

The vaccine prequalification dossier was submitted in a CTD format. The vaccine meets WHO Technical Report Series (e.g., TRS 999, Annex 4 “Recommendations to assure the quality, safety and efficacy of recombinant human papillomavirus virus-like particle vaccines”). In addition, the vaccine was found in compliance with WHO programmatic suitability criteria and labelling requirement.