Cecolin

Recombinant Human Papillomavirus Bivalent (Types 16, 18) Vaccine (*Escherichia coli*)

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cecolin is a mixture of two aluminum hydroxide adjuvant-adsorbed recombinant L1 capsid proteins of human papillomavirus (HPV) type-16 and type-18 each self-assembled into virus-like particles (VLPs). The HPV-16 and HPV-18 L1 antigens are expressed in Escherichia coli by recombinant DNA technology.

Active Substance:

Each dose (0.5ml) contains:

Recombinant human papillomavirus type 16 L1 protein	40μg
Recombinant human papillomavirus type 18 L1 protein	20μg

Excipients:

Aluminum hydroxide adjuvant, Sodium chloride, Sodium dihydrogen phosphate dihydrate, Disodium hydrogen phosphate dihydrate, Polysorbate 80 and Water for injection.

There are no preservative or antibiotics in Cecolin.

2. DESCRIPTION

The Recombinant Human Papillomavirus Bivalent (Types 16, 18) Vaccine (Escherichia coli) is manufactured by mixing purified HPV16 antigen bulk and purified HPV18 antigen bulk with aluminum adjuvant, to make bivalent antigen adsorbed bulk. The finished drug product is sterile white suspension filled into vials. Sedimentation of the HPV16/18 product may occur, and the product can be re-suspended by gently shaking. Each 0.5 mL dose contains 40 μg (80 μg/mL) of the recombinant HPV16 protein antigen and 20 μg (40 μg/mL) of the recombinant HPV18 protein antigen

3. PHARMACEUTICAL FORM

Cecolin is presented as 0.5 mL suspension for injection in a vial.

Upon storage, a fine white deposit with a clear colourless supernatant can be observed. Cecolin would be a suspension after thorough agitation.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cecolin is indicated for women aged 9-45 years.

At present, it has not been demonstrated that Cecolin has preventive effect on individual who had been infected by the vaccine types of HPV. The risk of exposure to HPV increases with age, especially after sexual debut. Therefore, it is recommended to vaccinate with Cecolin as early as possible. It would be more beneficial for women/girls to receive Cecolin at the earlier time between ages 9-45 years.

Cecolin is used for preventing the following diseases caused by oncogenic human papillomavirus (HPV) types 16 and/or 18 (see section 6):

- Cervical cancer
- Cervical intraepithelial neoplasia Grade 2 or 3 (CIN2/3) and adenocarcinoma in-situ (AIS)
- Cervical intraepithelial neoplasia Grade 1 (CIN1)

  And persistent infections of HPV types 16 and/or 18. The use of Cecolin should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Table 1 Vaccination Schedule

Age at the time of the first injection	Immunization and schedule
9 to and including 14 years*	2 doses (0.5 ml) 2nd dose 6 months after first
From 15 years and above**	3 doses (0.5 ml) at 0, 1 and 6 months*

*If flexibility in the vaccination schedule is necessary, the second dose can be injected within 1-2 months after the first dose, and the third dose can be injected within 5-8 months after the first dose. At present, it has not been determined whether the booster vaccination is required for Cecolin.
**It is recommended for women aged 27-45 years to consult with doctor before use this product (see Pharmacological Properties section).

Method of administration

1. Cecolin is injected intramuscularly and the preferred site for vaccination is deltoid muscle of upper arm. There has been no data on subcutaneous injection of Cecolin. Intravascular or intradermal injection is prohibited.
2. Cecolin should be shaken well before use, and it should be a white homogeneous suspension after shaking.
3. A separate sterile syringe and needle must be used for each vaccination.

4. Cecolin should be vaccinated as soon as possible after removal from the refrigeration container.

Any vial with crack, label unclear or invalid and vaccine with abnormal appearance should not be used.

4.3 Contraindications

1. Hypersensitivity to the active substances or to any of the excipients of the vaccine.
2. Individuals who develop symptoms indicative of hypersensitivity after receiving a dose of Cecolin.

4.4 Special warnings and precautions for use

1. Vaccination cannot replace the routine cervical cancer screening or other measures to prevent HPV infection and sexually transmitted diseases. Therefore, routine cervical cancer screening remains extremely important as recommended by the relevant health administrative departments.

2. Prior to the vaccination of Cecolin, medical personnel should inquire and review the vaccinee's medical history (especially the prior vaccination history and any prior adverse reaction related to vaccination), and conduct clinical examination to evaluate the benefits and risks of vaccination. Cecolin is not recommended for populations other than those described in section 4.1.

3. Like other vaccines for injection, appropriate medical emergency measures and monitoring methods should be prepared to ensure that those who develop allergic reactions after the injection of Cecolin can be promptly treated.

4. Syncope: syncope (fainting) may occur after any dose of vaccine, leading to falls and injuries, especially in adolescents and young adults. Therefore, it is recommended that the observation on site be conducted for at least 30 minutes after each injection as required in the vaccination procedures.

It has been reported that syncope associated with tonic-clonic seizures and other epileptiform seizures may occur after the vaccination with similar products overseas. Syncope associated with tonic-clonic seizures is usually transient, and it can be resolved spontaneously when the vaccinee is placed in a supine or head-down position and the cerebral perfusion is restored. Some vaccinees

may experience psychogenic reactions before/after the vaccination, and measures should be taken to avoid injury from the syncope.

5. Like other vaccines, the vaccination of Cecolin should be postponed in vaccinees with acute serious febrile illness. In case of current or recent fever symptoms, whether to postpone the vaccination depends mainly on the severity of the symptoms and their etiology. Low-grade fever and mild upper respiratory tract infection are not absolute contraindications to vaccination.

6. Cecolin should be used with caution in vaccinees with thrombocytopenia or any coagulation disorder.

7. Like any other vaccine, vaccination with Cecolin may not ensure the protective effect for all vaccinees.

8. Cecolin is only used for preventive purposes, but not indicated for the treatment of existing HPV-related lesions or preventing the progression of lesions.

9. Cecolin cannot prevent lesions caused by all high-risk types HPV infections. It has not been proved that Cecolin can prevent the lesions caused by the infection of non-vaccine types of HPV as well as the diseases not caused by HPV infection.

10. There has been no data on the use of Cecolin in vaccinees with impaired immune system (such as receiving the medication of immunosuppressive agents). Like other vaccines, vaccination of Cecolin in immunocompromised people may not induce adequate immune response.

11. At present, the maximum protective period of Cecolin has not been fully established.

4.5 Interaction with other medicinal products and other forms of interaction

1. Since no clinical trial has been conducted for the vaccination of Cecolin combined with other vaccines in China, there is currently not relevant research data available.

2. The use of immunoglobulin or blood products should be avoided within 3 months prior to the vaccination of Cecolin.

3. There has been no clinical evidence available to demonstrate whether the use of hormonal contraceptives will affect the preventive effect of Cecolin.

4. Like other vaccines, vaccination of Cecolin in immunocompromised people may not induce adequate immune response. Concomitant use with immunosuppressive agents may not induce an optimal active immune response.

5. At present, there has been no clinical data available to support the interchangeable use among Cecolin and other HPV vaccines.

6. Due to the lack of incompatibility studies, the injection of Cecolin combined with other medicinal products is prohibited.

4.6 Pregnancy and lactation

Pregnancy

1. At present, there has been no independent study conducted to systematically evaluate the effect of Cecolin on pregnant women. The very limited data (8 cases) from the clinical trial showed that the accidental vaccination of Cecolin during pregnancy does not cause abnormal pregnancy outcomes and neonatal health conditions, and no adverse effects on pregnancy rate, pregnancy outcomes and neonatal health conditions were observed after the vaccination of Cecolin. However, the data are not sufficient to determine whether pregnant women are at risk of adverse pregnancy (including spontaneous abortion) after the vaccination of Cecolin.

2. In animal experiments, no direct or indirect adverse effects on reproduction, pregnancy, embryo/fetus development, parturition or postnatal development are observed after the vaccination of Cecolin.

3. Vaccination of Cecolin should be avoided during pregnancy. If a woman is pregnant or preparing for pregnancy, it is recommended to postpone or interrupt the vaccination procedure, and the vaccination can be conducted after the end of pregnancy.

Lactating women

There has been no relevant study data to Cecolin used in lactating women

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive or use machines have been performed. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

According to the recommendations of the Council for International Organizations of Medical

Sciences (CIOMS), adverse reactions considered as being at least possibly related to vaccination have been categorised by frequency.

Frequencies are reported as:
Very common (≥10%),
Common (≥1% to <10%),
Uncommon (≥0.1% to <1%);

The adverse reactions of Cecolin are described as follows:

A total of 4316 female subjects aged 18-45 years and 754 female subjects aged 9-17 years were vaccinated with Cecolin in 3 clinical trials (phase II, phase III and bridging studies) conducted in China. The immediate reactions of the subjects within 30 minutes after each injection of Cecolin were observed and recorded on site; the adverse reactions/events within 30 days after each dose and all the serious adverse events during the observation period were recorded.

Table 2 Adverse Reactions Categorized by System Organ Class

System Organ Class	Frequency	Adverse reactions
Systemic Adverse Reactions		
General disorders and administration site conditions	Very common Common	Fever (≥37.1 ℃) Fatigue
Gastrointestinal disorders	Common	Nausea, vomiting and diarrhea
Nervous system disorders	Common	Headache and dizziness
Ear and labyrinth disorders	Uncommon	Vertigo
Skin and subcutaneous tissue disorders	Uncommon	Pruritus, rash and allergic dermatitis
Immune system disorders	Uncommon	Hypersensitivity
Respiratory, thoracic and mediastinal disorders	Common	Cough
Musculoskeletal and connective tissue disorders	Common	Muscle pain
Local Adverse Reactions		
General disorders and administration site conditions	Very common Common Uncommon	Injection site pain Injection site induration, injection site swelling, injection site pruritus, injection site erythema Injection site discomfort, injection site Rash

Reporting of suspected adverse reactions

The reporting of suspected adverse reactions is important for the evaluation of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to national regulatory authority for monitoring Adverse Events Following Immunisation (AEFI) or Adverse Drug Reactions. Where reporting to the national regulatory authority is not possible, please log in the official website of INNOVAX or send email to *sae@innovax.cn*.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties Clinical studies

Three clinical trials on Cecolin have been completed in China (Table 4) to evaluate its protective efficacy, immunogenicity (including pediatric population aged 9-14 years vaccinated with 2 doses), long-term protective effect and antibody persistence in female population aged 9-45 vaccinated with 3 doses of Cecolin.

Table 4 Summary of Major Clinical Studies Conducted in Female Population Aged 9-45 in China

Study Number	Phase	Study Design	Number of Subjects*	Subjects
HPV-PRO-002	Phase II	Randomized, double-blind, placebo-controlled clinical trial	1600	Females aged 18-25
HPV-PRO-003	Phase III	Randomized, double-blind, placebo-controlled and multicenter clinical trial	7372	Females aged 18-45
HPV-PRO-006	Bridging	Randomized and controlled clinical trial	979	Females aged 9-26

* Subjects at least vaccinated one dose.

Efficacy

In the trial for protective efficacy of HPV-PRO-003, a total of 7,372 women aged 18-45 years were enrolled. The interim analysis was conducted after confirmation through independent review by the Data Safety and Monitoring Board (DSMB) at a follow-up of 42 months (median

42.5 months). The protective efficacy against CIN2/3, AIS or cervical cancer associated with HPV-16 and/or HPV-18 in the per protocol set (PPS) population was 100.0% (95% CI: 55.6, 100.0). The efficacy in preventing different disease endpoints associated with HPV-16 and/or HPV-18 is shown in Table 5. In the PPS of this study, one case of VaIN1 occurred in the control group (combined occurrence of CIN2), while no case of VIN was found.

Table 5 Summary of Protective Efficacy of Cecolin against Different Disease Endpoints in Female Population Aged 18-45 Years (PPS Population*)

Study Endpoint	Cecolin		Control (Hepatitis E Vaccine)		Protective Efficacy % (95% CI)
	N	Number of Cases	N	Number of Cases	
HPV type 16 and/or 18 infection-related high-grade precancerous lesions (CIN2/3 or AIS)	3306	0	3296	10	100.0 (55.6, 100.0)
HPV type 16 and/or 18 infection-related precancerous lesions (CIN1/2/3 or AIS)	3306	0	3296	14	100.0 (70.0, 100.0)
Persistent infection with HPV 16 and/or 18 (over 6 months)	3240	1	3246	45	97.8 (87.1, 99.9)
Persistent infection with HPV 16 and/or 18 (over 12 months)	3200	1	3199	22	95.5 (72.2, 99.9)

Note: N= number of subjects included in the analysis.

*PPS population must simultaneously meet the following conditions: subjects completed all 3 doses of vaccination after the enrollment; subjects had no major protocol violation; subjects were negative for neutralizing antibody against relevant vaccine HPV types on the day of enrollment and the same HPV type DNA from the day of enrollment to 1 month after the last vaccination, completed the gynecological visit sufficient to support the determination of endpoint indicators 1 month after the last vaccination, and received the evaluation of efficacy from 1 month after the last vaccination.

Efficacy against HPV-16/18 in women with evidence of HPV-16 or HPV-18 infection at study entry.

There was no evidence showing that Cecolin has a protective effect from disease caused by the HPV types for which subjects were HPV DNA positive at baseline. However, subjects already infected (HPV DNA positive) with one of the vaccine-related HPV types prior to vaccination were protected from infection or lesions caused by the other vaccine HPV type.

Efficacy against HPV types 16 and 18 in women with and without prior infection or disease

The Intention-to-treat set (ITT) included all subjects who received at least one dose of the vaccine, irrespective of their HPV DNA status, cytology and serostatus at baseline. This cohort included women with or without current and/or prior HPV infection.

Vaccine efficacy against high grade cervical lesions and virological endpoints (persistent infection) related to HPV 16/18 observed in ITT at the end of study was as follows:

- CIN2+: 18.2% (95%CI: -47.3, 55.0)
- 6-month persistent infection: 78.2% (95%CI: 61.4, 88.4)
- 12-month persistent infection: 67.8% ((95%CI: 36.8, 84.7)

Efficacy against HPV types other than HPV 16 and HPV 18

For subjects who were negative for infection of corresponding type at baseline, it was found that except HPV 16 and HPV 18, the vaccine had no statistically significant protective effects from other 12 high-risk (HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) persistent infection (over 6 months) or CIN2+ and/or VIN2+ and/or VaIN2+ lesions related to the above infections.

Efficacy in women aged 27 to 45 years

In the multi-center, double-blind, randomised Phase III clinical trial (HPV-PRO-003), a total of 3649 subjects age 27-45 years were enrolled. The efficacy of Cecolin against virology endpoints are presented in the following table:

Table 6 Efficacy of Cecolin against Virology Endpoints

HPV16/18 endpoint	PPS[a]			ITT[b]		
	Cecolin	Control	%Efficacy（95%CI）	Cecolin	Control	%Efficacy（95%CI）
	n/N	n/N		n/N	n/N	
PI (6m+)	0/1678	26/1664	100.0 (85.2, 100.0)	6/1782	32/1782	81.5 (55.2, 93.7)
PI (12m+)	0/1666	14/1652	100.0 (70.6, 100.0)	4/1771	18/1767	78.1 (33.4, 94.6)

N= number of subject in each group
n= number of subjects reporting at least one event in each group
PI (6M+) = 6-month (or above) persistent infection
PI (12M+) = 12-month (or above) persistent infection
CI= Confidence Interval
a: During full-schedule, no major protocol violations occurred, at least one valid lesion endpoint visit after M7, negative serum neutralizing antibodies of corresponding type of HPV at D0, HPV DNA negative for the corresponding type at D0 and M7, the number of cases calculated after M7.
b: All subjects who received at least one dose of the vaccine, irrespective of their HPV DNA status, cytology and serostatus at baseline. This cohort included women with or without current and/or prior HPV infection.

Immunogenicity

Immunogenicity in Female Population Aged 18-45

In the HPV-PRO-003 efficacy trial, the immunogenicity results at 7 months and 42 months of subjects who were negative for neutralizing antibody against vaccine types of HPV before immunization and fully received 3 doses of test vaccine are shown in Table 7.

Table 7. Immunogenicity in Women Aged 18-45*

Time	HPV 16			HPV 18		
	Positive Number/ Observed Number	Positive Rate (%)	GMC (IU/ml) (95% CI)	Positive Number/ Observed Number	Positive Rate (%)	GMC (IU/ml) (95% CI)
7th month	116/116	100.00 (96.87, 100.00)	726.76 (638.49, 827.24)	125/125	100.00 (97.09, 100.00)	435.47 (378.02, 501.64)
42th month	111/111	100.00 (96.73, 100.00)	75.48 (62.38, 91.32)	117/119	98.32 (94.06, 99.80)	35.41 (29.12, 43.05)

*As shown in the table, neutralizing antibody is used to evaluate the immunogenicity of Cecolin. The detection method of neutralizing antibody is Pseudovirus-based Neutralization Assay (PBNA), which is quantified by using the international standards of National Institute for Biological Standards and Control (NIBSC). The positive cut-off values of neutralizing antibodies against HPV type 16 and HPV type 18 are 3.1 IU/ml and 2.0 IU/ml, respectively.

Immunogenicity in Female Population Aged 9-17 in the Bridging Study

In the bridging study of HPV-PRO-006, which included females aged 9-14 y receiving 2 doses, females aged 9-17 y receiving 3 doses and females aged 18-26 y receiving 3 doses, the GMCs of the above 3 populations in the bridging study met the non-inferiority criterion (the lower limit of the 95% CI of the GMC ratio was greater than 0.5) compared with the women aged 18-26 y in the phase III trial.

Studies on the immune persistence in the population aged 9-17 y vaccinated with Cecolin are ongoing.

Table 8 Immunogenicity Results in the Population Aged 9-17 and in the Population Aged 18-26 of Phase III Trial

Variable	Phase III		Bridging					
	18-26 years#	N	Age of 9-14 (2-dose group)	N	Age of 9-17 (3-dose group)	N	18-26 years#	N
Seroconvertion Rate % (95%CI)								

HPV16	100.00 (94.04, 100.00)	60	100.00 (98.75, 100.00)	293	100.00 (99.14, 100.00)	429	100.00 (98.07, 100.00)	189
HPV18	100.00 (94.31, 100.00)	63	100.00 (98.75, 100.00)	293	100.00 (99.14, 100.00)	425	99.49 (97.22, 99.99)	198
(GMC) (95% CI)								
HPV16	778.72 (658.35, 921.11)	60	1466.25 (1338.54, 1606.15)	293	1903.28 (1774.19, 2041.76)	429	1011.52 (900.38, 1136.38)	189
HPV18	495.82 (402.45, 610.85)	63	606.70 (555.03, 663.18)	293	1099.48 (1014.53, 1191.54)	425	503.01 (442.90, 571.28)	198

Although the subjects in phase III and bridging studies were both the population aged 18-26, the subjects came from different studies and different regions, and the specific age composition was different (the proportion of subjects aged 18-22 in bridging study was relatively larger), there was a slight difference without statistical significance in antibody GMC between the two trials.

Immunogenicity in HIV infected women

Not studied.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

See section 1.

6.2 Incompatibilities

In the absence of compatibility studies, Cecolin must not be mixed with other medicinal products.

6.3 Shelf Life

36 months.

6.4 Special precautions for storage

Cecolin must be stored at 2°C to 8°C (36ºF and 46ºF) and protected from light. DO NOT FREEZE. Discard if vaccine has been frozen.

6.5 Nature and contents of container

Cecolin is supplied as a carton of ten single-dose vial (size: 2 mL, type I borosilicate glass, with a rubber butyl stopper).

6.6 Special precautions for disposal and other handling

Cecolin should be shaken well before use, and it should be a white homogeneous suspension after shaking.

6.7 Vaccine Vial Monitor

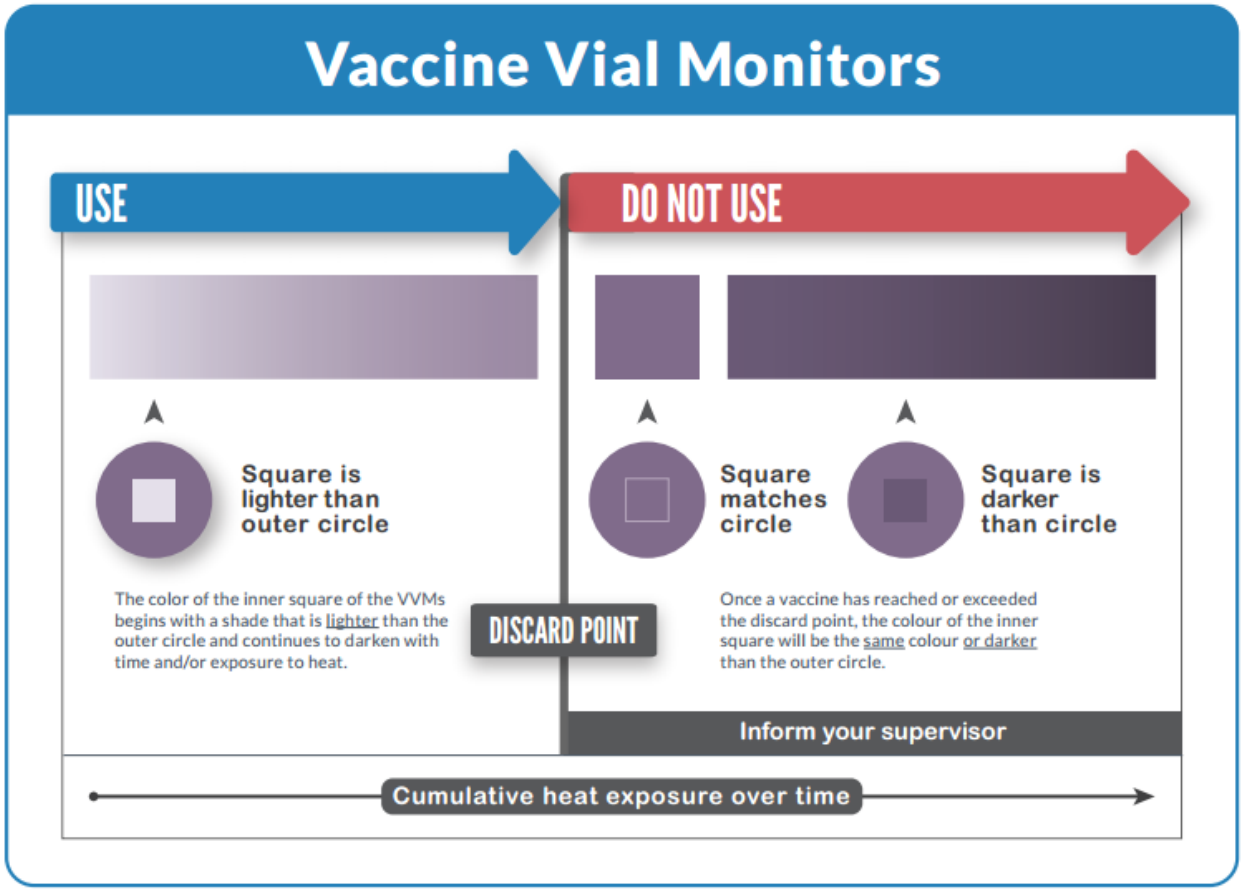
This infographic summarises how health workers can use VVMs to decide whether or not to use a vaccine vial. It presents VVM colour change as a continuous progression, rather than as four distinct stages, and can be included in guidance and training materials.

7. PRESENTATION

BOX, 10 vials @ 0.5ml ; Reg No: DKI ……

HARUS DENGAN RESEP DOKTER

Pada Proses Pembuatannya Bersinggungan dengan Bahan Bersumber Babi



INDONESIA Package Insert Version number: 01 Date of Issue: © [2022] Xiamen Innovax Biotech Co., Ltd.
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