SUMMARY OF PRODUCT CHARACTERISTIC

1. Name of the Medicinal Product

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

Trade Name: Cecolin

2. Qualitative and Quantitative Composition

Cecolin is a mixture of two aluminum hydroxide adjuvant-absorbed 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

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Suspension for injection.

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

4. Clinical Particulars

4.1 Therapeutic indication

Cecolin is indicated for women aged 9-45 years.

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

- 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.

See sections 4.4 and 5.1 for important information on the data that support these indications.

The use of Cecolin should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

1). It is recommended to receive 3 doses of Cecolin of 0.5-mL each, by intramuscular injection according to the following schedule: 0, 1, and 6 months.

According to the clinical trial results of Cecolin , 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.

2). On the basis of the clinical trial results of Cecolin (see section 5.1) and refer to the recommendations in *Human Papillomavirus Vaccines: WHO Position Paper (2017),* female aged 9-14 years can also choose a vaccination schedule of two doses at 0 month and 6 month (0.5-ml per dose, with an interval of not less than 5 months).

3). At present, it has not been determined whether the booster vaccination is required for Cecolin .

Method of administration

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.

For instructions on the handling of the vaccine before administration, see section 6.6.

4.3 Contraindication

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 warning and precaution 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 [Therapeutic indications] of the package insert.

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. In the phase III clinical trial of Cecolin , the mean follow-up period for the protective potency against pathological high-grade lesions (such as CIN2/3 and AIS) is 66 months (median: 68.7 months), and the mean follow-up period for the persistence of neutralizing antibodies is 66 months (median: 69.4 months). See section 5.1 for specific results.

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

Pregnant Women:

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 . As many drugs can be secreted in breast milk, Cecolin should be used with caution in lactating women.

4.7 Effect 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

According to the recommendations of the Council for International Organizations of Medical Sciences (CIOMS), the incidence rate is expressed as: very common (≥10%), common (1~10%, 1% inclusive), and uncommon (0.1~1%, 0.1% inclusive); and the adverse reactions of Cecolin are described as follows:

(1) Clinical Trial

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 (~66 months) were recorded. The following solicited and unsolicited adverse reactions were observed:

Systemic Adverse Reactions

Very common: Fever (≥37.1 °C)

Common: Headache, fatigue, cough, muscle pain, nausea, diarrhea, dizziness and vomiting

Uncommon: Hypersensitivity, allergic dermatitis, rash, vertigo and pruritus

Local Adverse Reactions

Very common: Pain at the injection site

Common: Pruritus, induration, swelling and erythema at injection site

Uncommon: Rash and discomfort at injection site

Most of the above adverse reactions are mild to moderate.

(2) Domestic and Overseas Clinical Trials of Similar Products

In addition to the above adverse reactions, the following systemic adverse reactions are observed in the domestic and overseas clinical trials of similar products: abdominal pain, arthralgia, back pain, musculoskeletal pain, neck pain, pain in extremity, axillary pain, lymphadenopathy, urticaria, pityriasis rosea, eyelid edema, upper respiratory tract infection, dyspnea, chills, flu-like symptoms, nasopharyngitis, nasal congestion, oropharyngeal pain, gastroenteritis, dyspepsia, migraine, malaise, somnolence, syncope, irregular uterine bleeding, dysmenorrhea, cough, hyperhidrosis. Local adverse reactions include bruises, hemorrhage, hematoma, allergy, papules, paresthesia and scar at the injection site.

(3) Post-marketing Surveillance of Similar Products

In addition to the safety information mentioned above, the safety data obtained from the post-marketing surveillance of similar products in China and overseas (these data are voluntarily reported by uncertain population and cannot accurately evaluate the incidence rate or determine the relationship with the vaccination) are as follows:

Immune system: Idiopathic thrombocytopenic purpura, bronchospasm, and angioedema;

Nervous system: Syncope or vasovagal reaction (sometimes accompanied by tonic-clonic seizures), acute disseminated encephalomyelitis (ADEM) (occurring about several days to 2 weeks after vaccination, or accompanied by fever, headache, convulsions, movement disorders, or disturbance of consciousness), and Guillain–Barré syndrome (manifested as flaccid paralysis starting from the distal extremities, decreased or absent tendon reflexes)

Infections and infestations: Cellulitis

Others: The vaccine may experience severe pain (such as muscle pain, joint pain and skin pain), numbness and powerlessness, which are not limited to the injection site and last for a long time; the mechanism has not been identified yet.

4.9 Overdose

No case of overdose has been reported.

5. Pharmaceutical properties

5.1 Pharmacodynamics properties

Three clinical trials on Cecolin have been completed in China (Table 1) 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 1 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.

1. 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: 55.7, 100.0). The efficacy in preventing different disease endpoints associated with HPV-16 and/or HPV-18 is shown in Table 2. 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.

During the follow-up after interim analysis until month 66 (median month 68.7), 3 new cases of CIN2+ were observed in the PPS and all of them occurred in the control group. See

the following table for details.

Table 2 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)	3277	0	3261	10	100.0 (55.7, 100.0)
HPV type 16 and/or 18 infection-related precancerous lesions (CIN1/2/3 or AIS)	3277	0	3261	14	100.0 (70.0, 100.0)
Persistent infection with HPV 16 and/or 18 (over 6 months)	3211	1	3212	42	97.7 (86.2, 99.9)
Persistent infection with HPV 16 and/or 18 (over 12 months)	3171	1	3165	21	95.3 (70.7, 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 protective potency from 1 month after the last vaccination.

2. Immunogenicity

(1) Immunogenicity in Female Population Aged 18-45

In the HPV-PRO-003 efficacy trial, the immunogenicity results at 7 months, 42 months and 66 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 3.

Table 3. Immunogenicity in Women Aged 18-45 [*]

Timepoint	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	100.0 (96.9, 100.0)	726.76 (638.49, 827.24)	125/125	100.0 (97.1, 100.0)	435.47 (378.02, 501.64)
42th month	111/111	100.0 (96.7, 100.0)	75.48 (62.38, 91.32)	117/119	98.3 (94.1, 99.8)	35.41 (29.12, 43.05)
66th month	110/110	100.0 (96.7, 100.0)	71.42 (59.47, 85.78)	118/120	98.3 (94.1, 99.8)	33.78 (27.65, 41.28)

* As seen from 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.

(2) Immunogenicity in Female Population Aged 9-17 in the Bridging Trial

In the bridging trial of HPV-PRO-006, which included females aged 9-14 receiving 2 doses, females aged 9-17 receiving 3 doses and females aged 18-26 receiving 3 doses, the GMCs of the above 3 populations in the bridging trial 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 in the phase III trial.

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

Table 4. 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	100.0 (94.0, 100.0)	60	100.0 (98.7, 100.0)	291	100.0 (99.1, 100.0)	422	100.0 (98.0, 100.0)	181
HPV18	100.0 (94.3, 100.0)	63	100.0 (98.7, 100.0)	287	100.0 (99.1, 100.0)	424	100.0 (98.1, 100.0)	196
(GMC) (95%CI)								
HPV16	778.7 (658.3, 921.1)	60	1377.5 (1251.2, 1516.5)	291	1805.2 (1680.6, 1939.0)	422	942.8 (834.2, 1065.6)	181
HPV18	495.8 (402.4, 610.9)	63	708.1 (647.5, 774.4)	287	1335.3 (1228.1, 1451.7)	424	601.8 (530.6, 682.6)	196

Although the subjects in phase III and bridging trials 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 trial was relatively larger), there was a slight difference without statistical significance in antibody GMC between the two trials.

5.2 Pharmacokinetics properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of acute and repeated dose toxicity, local tolerance, reproductive and developmental toxicity (stage A, B, C, D) and systemic anaphylaxis.

6. Pharmaceutical particulars

6.1 List of excipients

Aluminum Hydroxide Adjuvant
Disodium Hydrogen Phosphate Dihydrate
Sodium Dihydrogen Phosphate Dihydrate
Sodium Chloride
Polysorbate 80
Water for Injection

6.2 Incompatibilities

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

6.3 Shelf life

36 months.

6.4 Special precaution 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 content 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

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

2). A separate sterile syringe and needle must be used for each vaccination.

3). 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.

7. Marketing authorization holder

Xiamen Innovax Biotech Co., Ltd.

8. Marketing authorization number(s)

08390/10410/NMR/2022

9. Date of first authorization / renewal of the authorization

Date of first authorization: December 30, 2019

10. Date of revision of the text

February 23, 2022