CERVAVAC®
Quadrivalent Human Papillomavirus (Serotype 6, 11, 16 & 18) Vaccine Recombinant

1 NAME OF THE MEDICINAL PRODUCT

CERVAVAC® Suspension for injection
Quadrivalent Human Papillomavirus (Serotypes 6, 11, 16 & 18) Vaccine (Recombinant)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose of 0.5 ml contains:

Human Papillomavirus type 6 L1 protein ≥ 20 mcg

Human Papillomavirus type 11 L1 protein ≥ 40 mcg

Human Papillomavirus type 16 L1 protein ≥ 40 mcg

Human Papillomavirus type 18 L1 protein ≥ 20 mcg

Al^{+++} ≤ 1.25 mg

Produced from strain: *Hansenula polymorpha*

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suspension for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CERVAVAC® is indicated in girls and women 9 through 26 years of age for the prevention of the following diseases caused by Human Papillomavirus (HPV) types, included in the vaccine:

• Cervical, vulvar, vaginal, and anal cancer caused by HPV types 16 and 18

• Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18:

• Cervical intraepithelial neoplasia (CIN) grade 2/3 and Cervical adenocarcinoma *in situ* (AIS)

• Cervical intraepithelial neoplasia (CIN) grade 1

• Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3

• Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
• Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

CERVAVAC® is indicated in boys and men 9 through 26 years of age for the prevention of the following diseases caused by HPV types included in the vaccine:

• Anal cancer caused by HPV types 16 and 18
• Genital warts (condyloma acuminata) caused by HPV types 6 and 11
And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18:
• Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

4.2 Posology and method of administration

Posology
Individuals 9 to 14 years of age
CERVAVAC® should be administered according to a 2-dose schedule (0.5 ml at 0, 6 months).

Individuals 15 to 26 years of age
CERVAVAC® should be administered according to a 3-dose (0.5 ml at 0, 2, 6 months) schedule.
The second dose should be administered at least one month after the first dose and the third dose should be administered at least 3 months after the second dose. All three doses should be given within a 1-year period.
The use of CERVAVAC® should be in accordance with official recommendations.

Pediatric population
The safety and efficacy of CERVAVAC® in children below 9 years of age have not been established. No data are available.
It is recommended that individuals who receive a first dose of CERVAVAC® complete the vaccination course with CERVAVAC®.
The need for a booster dose has not been established.
Method of Administration
CERVAVAC® should be administered intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.
CERVAVAC® must not be injected intravascularly, subcutaneous or intradermally. These methods

of administration are not recommended.

The vaccine should be used as supplied; no dilution or reconstitution is necessary. The full recommended dose of the vaccine should be used.

Shake well before use. Thorough agitation immediately before administration is necessary to maintain suspension of the vaccine. After thorough agitation, CERVAVAC® is a whitish turbid suspension.

Parenteral drug products should be inspected usually for particulate matter and discoloration prior to administration. Discard the product if particulates are present or if it appears discolored.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients of the vaccine.

Hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after a previous dose of CERVAVAC®.

4.4 Special warnings and special precautions for use

As with any vaccine, vaccination with CERVAVAC® may not result in protection in all vaccine recipients.

CERVAVAC® is for prophylactic use only and has no effect on active HPV infections or established clinical disease. This vaccine is not intended to be used for treatment of active external genital lesions; cervical, vulvar, or vaginal cancers; CIN, VIN, VaIN. This vaccine will not protect against disease that are not caused by HPV.

CERVAVAC® has not been demonstrated to protect against diseases due to HPV types not contained in the vaccine. Therefore, appropriate precautions against sexually transmitted diseases should continue to be used.

Vaccination is not a substitute for routine cervical screening. Since no vaccine is 100% effective and CERVAVAC® will not provide protection against every HPV type, or against existing HPV infections, routine cervical screening remains critically important and should follow local recommendations. As with all injectable vaccines, appropriate medical treatment should always be readily available in case of rare anaphylactic reactions, following the administration of the vaccine.

The decision to administer or delay vaccination because of a current or recent febrile illness depends largely on the severity of the symptoms and their etiology. Low-grade fever and mild upper

respiratory infection are not generally contraindications to vaccination.

Individuals with impaired immune responsiveness, whether due to the use of immunosuppressive therapy, a genetic defect, Human Immunodeficiency Virus (HIV) infection, or other causes, may have reduced antibody response to active immunization.

This vaccine should be given with caution to individuals with thrombocytopenia or any coagulation disorder because bleeding may occur following an intramuscular administration in these individuals.

Syncope

Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 30 minutes after administration is recommended. It is important that procedures are in place to avoid injury from faints. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position.

4.5 Interaction with other medicinal products and other forms of interaction

CERVAVAC® can be given concomitantly with combined booster vaccine containing diphtheria (d), tetanus (T), pertussis (acellular) with or without Poliomyelitis (inactivated) vaccine. It can also be given concomitantly with Hepatitis B, Hepatitis A, Meningococcal Vaccine. When CERVAVAC® is administered concomitantly with other injectable vaccines, they should be given with separate syringes and at different injection sites. It should not be mixed with any other vaccine in the same syringe or vial.

There are no data on the concomitant use of potent immunosuppressants with CERVAVAC®. Individuals receiving therapy with immunosuppressive agents (systemic doses of corticosteroids, antimetabolites, alkylating agents, cytotoxic agents) may not respond optimally to active immunization.

4.6 Fertility, pregnancy and lactation

Fertility

No human data from prospective clinical studies are available.

Pregnancy

CERVAVAC® is not to be used during pregnancy. Women who are pregnant or trying to become pregnant, are advised to postpone or interrupt vaccination until completion of pregnancy.

Lactation

It is not known whether the vaccine antigens or antibodies induced by the vaccine are excreted in human milk. CERVAVAC® can be administered to 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.

4.8 Undesirable effects

Summary of the safety profile

The safety profile presented below is based on data from clinical trial (SII-qHPV/IN-02) conducted in India where CERVAVAC® was administered to 1530 study participants aged 9 through 26 years. The most common events occurring after CERVAVAC® administration were injection site pain, and headache. The majority of adverse events were mild to moderate in severity and usually resolved within a few days of vaccination. All resolved without sequelae.

Tabulated list of adverse reactions:

Adverse events are organized by MedDRA System Organ Class (SOC). Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse events are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000) and very rare (<1/10,000).

Table 1: Adverse reactions reported in clinical trial with CERVAVAC®

System Organ Class	Frequency	Adverse Reactions
Nervous system disorders	Very Common	Headache
	Common	Dizziness
Gastrointestinal disorders	Common	Nausea
Skin and subcutaneous tissue disorders	Common	Injection Site Pruritus
Musculoskeletal and connective tissue disorders	Common	Pain in Extremity
General disorders and administration site conditions	Common	Injection site erythema
	Very Common	Injection site pain
	Common	Injection site swelling
	Common	Pyrexia

4.9 Overdose

No cases of overdose were reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Viral Vaccines, Papillomavirus vaccines, ATC code: J07BM01

Mechanism of action:

CERVAVAC® contains Human Papillomavirus Quadrivalent (Serotypes 6, 11, 16, 18) L1 virus like particles (VLPs), which are proteins that resembles wild type virion. Because the VLP contains no viral DNA, they cannot infect cells or reproduce or cause disease. Animal studies with analogous animal papillomaviruses suggest that the efficacy of L1 VLP vaccines may involve the development of humoral immune responses. Human beings develop a humoral immune response to the vaccine, although the exact mechanism of protection is unknown.

Immune response:

The minimum anti-HPV titer that confers protective efficacy has not been established. The antibody response to all 4 HPV types (Serotypes 6, 11, 16, 18) was measured using a multiplex VLP-based immuno assay on the meso scale discovery platform which was demonstrated to correlate with the pseudovirion-based neutralisation assay (PBNA).

CERVAVAC® has been evaluated in a randomized controlled clinical trial and has demonstrated comparable immunogenicity against licensed quadrivalent vaccine when administered to female and male aged 9-26 yrs.

In a pivotal, phase 2/3, multicentric, randomized, controlled study (SII-qHPV/IN-02) in 9-26 years aged population, CERVAVAC® has demonstrated robust antibody response. Vaccine-induced IgG Geometric Mean Titres (GMT) were > 1000 times higher than the baseline titres against all targeted HPV types. Post vaccination, at 7-month timepoint (1 month after the last dose), a 100% seroconversion was reported across all 4 vaccine types (Serotypes 6, 11, 16, 18) in initially seronegative populations defined by age range. Anti HPV Geometric Mean Titres (GMT) at 7 months among girls/boys aged 9-14 years and women/men aged 15-26 years are provided in Table 2.

Table 2: Summary of anti HPV GMTs in girls/women and boys/men

Population	CERVAVAC®		
	n	Pre-vaccination	Post-vaccination
		GMT (98.75% CI)	GMT (98.75% CI)
Anti HPV 6			
9 to 14 yrs Girls	350	0.06	304.08
		(0.06, 0.08)	(272.92, 338.80)
9 to 14 yrs Boys	349	0.07	288.41
		(0.05, 0.08)	(256.61, 324.14)
15 to 26 yrs Women	343	0.07	142.96
		(0.06, 0.09)	(128.06, 159.60)
15 to 26 yrs Men	346	0.07	137.90
		(0.05, 0.08)	(121.65, 156.31)
Anti HPV 11			
9 to 14 yrs Girls	350	0.04	339.11
		(0.03, 0.05)	(305.74, 376.12)
9 to 14 yrs Boys	349	0.04	305.25
		(0.03, 0.05)	(271.49, 343.21)
15 to 26 yrs Women	343	0.05	122.36
		(0.04, 0.06)	(109.49, 136.76)
15 to 26 yrs Men	346	0.04	108.01
		(0.03, 0.05)	(95.65, 121.98)
Anti HPV 16			
9 to 14 yrs Girls	350	0.08	1335.64
		(0.06, 0.10)	(1176.25, 1516.63)
9 to 14 yrs Boys	349	0.10	1161.13
		(0.08, 0.13)	(1009.90, 1334.00)
15 to 26 yrs Women	343	0.11	547.72
		(0.08, 0.15)	(488.97, 613.52)
15 to 26 yrs Men	346	0.10	551.36
		(0.08, 0.13)	(483.31, 628.99)
Anti HPV 18			
9 to 14 yrs Girls	350	0.20	526.25
		(0.16, 0.25)	(460.85, 600.93)
9 to 14 yrs Boys	349	0.22	440.75
		(0.18, 0.27)	(384.52, 505.20)
15 to 26 yrs Women	343	0.25	278.96
		(0.20, 0.31)	(245.46, 317.04)
15 to 26 yrs Men	346	0.23	266.58

		(0.18, 0.28)	(229.93, 309.07)

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

Animal Toxicity studies

Non-clinical data reveal no special hazard for humans based on a conventional study of acute and repeat dose toxicity.

Reproductive tox studies

Non-clinical data obtained with CERVAVAC® reveal no specific hazard for humans based on female fertility, early embryonic development and prenatal development studies in animals.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride

Polysorbate 80

L-Histidine

Water for Injections (WFI)

6.2 Incompatibilities

The vaccine is not to be mixed with other vaccines/products in the same syringe.

6.3 Shelf-life

Unopened vial: 36 months

Once opened, multi-dose vials should be used as soon as practically possible and within 6 hours when kept between +2ºC and +8ºC. All opened multidose vials of CERVAVAC® should be discarded at the end of immunization session or within six hours, whichever comes first.

6.4 Special precautions for storage

Store in a refrigerator (+2° to +8°C).

Do not freeze.

Store in an original package in order to protect from light. For storage condition, after first opening of the medicinal product, see Section 6.3.

6.5 Nature and contents of container

Single dose vial

Multidose vial (2 doses)

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORIZATION

Serum Institute of India Pvt. Ltd.
212/2, Hadapsar, Pune-411028, INDIA.

8 MARKETING AUTHORISATION NUMBER (S)

Permission No.: MF/BIO/22/000072

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Permission No.: MF/BIO/22/000072 dated 12-July-2022

Manufacturing License number: 10

Date: 31 December 2022