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WALVAX®
Yuxi Zerun Biotechnology Co., Ltd.

Recombinant Human Papillomavirus Bivalent (Types 16, 18) Vaccine (*Pichia pastoris*)

Please read the instructions carefully and use them under the guidance of doctors

【Drug Name】

WALRINVAX®

Recombinant Human Papillomavirus Bivalent (Types 16, 18) Vaccine (*Pichia pastoris*)

【Ingredients and Description】

WALRINVAX® is a recombinant bivalent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV types 16 and 18. The L1 proteins are produced by separate fermentations in recombinant *Pichia pastoris* and self-assembled into VLPs. The purified VLPs are adsorbed on aluminum phosphate adjuvant.WALRINVAX® is a milky white suspension, which forms shakable fine white precipitate after storage.

Active ingredients: each 0.5 mL dose contains 40 μg of HPV16L1 protein and 20 μg of HPV18L1 protein

Adjuvant: each 0.5 mL dose contains 225 μg of aluminum (as aluminum phosphate)

Excipients: sodium chloride, histidine, polysorbate 80, and water for injection

There are no preservatives or antibiotics in WALRINVAX®.

【Indication】

WALRINVAX® is approved for use in females 9 through 30 years of age.

WALRINVAX® has not been demonstrated to provide protection against disease from vaccine HPV types to which an individual has previously been exposed. The risk of exposure to HPV increases with age, especially after sexual debut. Therefore, it is recommended to vaccinate as early as possible.

【Clinical Use】

WALRINVAX® is indicated for the prevention of the following diseases caused by high-risk HPV Types 16, 18 (see [Clinical Trials] for details):

• Cervical cancer

• Cervical intraepithelial neoplasia (CIN) grade 2 or grade 3 and cervical adenocarcinoma in situ (AIS)

【Specification】

0.5 mL/vial. Each dose (0.5 mL) contains 40 μg of HPV 16 L1 protein and 20 μg of HPV 18 L1 protein.

【Dosage and Administration】

1.Each dose of WALRINVAX® is 0.5-mL.

2.Administer WALRINVAX® as follows:

Age	Regiment	Immunization and schedule
9 through 14 years	2-dose*	0, 6 months
	3-dose**	0, 2, 6 months
15 through 30 years	3-dose**	0, 2, 6 months

* The interval between the first and the second dose is not less than 5 months

** The second dose could be vaccinated within 2 to 3 months after the first dose, and the third dose could be vaccinated within 6 to 7 months after the first dose.

3.The need for a booster dose has not been established.

Vaccination Instructions

1.WALRINVAX® is administered intramuscularly and the preferred site of administration is the deltoid region of the upper arm. Do not administer this product intravenously, intradermally, or subcutaneously.

2.WALRINVAX® should be administrated as soon as possible after being removed from the refrigeration.

3.With thorough agitation, WALRINVAX® is a homogeneous milky white suspension.

4.Withdraw the 0.5 mL dose of vaccine from the single-dose vial using a sterile needle and syringe.

【Adverse Reactions】

1. Clinical trials

The safety of WALRINVAX® was evaluated in four clinical studies in China. The four studies included 7,371 females 9 through 30 years of age who received at least one dose of WALRINVAX®, including 921 females 9 through 17 years of age and 6,450 females 18 through 30 years of age. The immediate reactions within 30 minutes after each dose, the adverse events within 30 days after each dose, and all serious adverse events during the observation period (48 months after the first dose) were recorded.

According to the recommendations of the Council for International Organizations of Medical Sciences (CIOMS), the incidences of adverse reactions are expressed as follows: very common (≥ 10%), common (1% to 10%, including 1%), uncommon (0.1% to 1%, including 0.1%), rare (0.01% to 0.1%, including 0.01%) and very rare (< 0.01%). The adverse reactions of the vaccine are described as follows:

• Systemic adverse reactions

Very common: fever

Common: headache, fatigue, nausea, vomiting, myalgia, diarrhea

Uncommon: hypersensitivity, menstrual disorder, dizziness

Rare: Hypoaesthesia, vaginal haemorrhage, abdominal pain, abdominal pain lower, rhinorrhoea, nasal obstruction, oropharyngeal pain, oropharyngeal discomfort, tachycardia, chest pain, upper respiratory tract infection, pharyngitis, nasopharyngitis, herpes viral infections, erythemas, rash, acne, back pain, arthralgia, insomnia, fear of injection, asthenopia.

• Injection site adverse reactions

Very common: injection site pain

Common: pruritus, swelling, erythema, induration

Rare: Vaccination site paraesthesia

These adverse reactions usually were mild or moderate in intensity.

2. Clinical trials of similar products in China and abroad

In addition to the above-mentioned adverse reactions, the following have been observed in clinical trials of similar products in China and abroad.

Systemic adverse reactions: cough, dyspnea, nasal congestion, malaise, influenza like illness, axillary pain, chills, hyperhidrosis, dermatitis allergic, pruritus, urticaria, pityriasis rosea, vertigo, migraine, somnolence, syncope, intermenstrual bleeding, dysmenorrhoea, gastroenteritis, dyspepsia, neck pain, pain in extremity, lymphadenopathy, and eyelid oedema

Injection site reactions: bruising, haemorrhage, haematoma, papule, and injection site scar.

3. Post-marketing surveillance of similar products

In addition to the safety information in the above clinical trials, the following safety data were obtained by referring to the post-marketing monitoring of similar products in China and abroad. Because these data were from spontaneous reports, and the reported population size was uncertain, it is usually impossible to accurately estimate the incidences, and it cannot be confirmed that they are related to the use of the vaccine:

Immune system disorders: bronchospasm, angioedema

Nervous system disorders: acute disseminated encephalomyelitis, Guillain-Barre syndrome, Vasovagal syncope (sometimes accompanied by tonic-clonic seizures)

Infections and infestations disorders: cellulitis

Blood and lymphatic system disorders: primary thrombocytopenic purpura

Others: The vaccine recipients may experience severe pain (such as myalgia, arthralgia and skin pain) not limited to the injection site, numbness and powerlessness. These adverse events may last for a long period of time, but their pathogenic mechanisms are not yet clear.

【Contraindications】

1.Hypersensitivity to the active substances or to any of the excipients of the vaccine (see 【Ingredients and Description】for details).

2.Individuals who develop severe allergic reaction after receiving a dose of WALRINVAX® should not receive further dose of WALRINVAX®.

【Special Warnings and Precautions for Use】

1.Vaccination cannot replace routine cervical cancer screening, nor can it replace other measures to prevent HPV infection and sexually transmitted diseases. Therefore, it is important to routinely perform cervical cancer screening in accordance with the recommendations of the relevant health administrative departments.

2.Prior to the administration of WALRINVAX®, medical personnel should check whether the packaging container, label, appearance, and expiry date meet the requirements. Discard the vaccine, if the packaging container has cracks, the stopper is loose, the label is peeled off, particulate matter or discoloration in the vial, and the expiration date is exceeded.

3.Like other vaccines for injection, appropriate medical emergency measures and supervision should be readily available in place, to ensure that those who have allergic reaction after vaccination can be promptly treated.

4.Syncope (fainting) may occur after vaccination, leading to falls and injuries, especially among adolescents and young adults. Therefore, it is recommended to observe the recipients on the site for at least 30 minutes after each injection.

It has been reported that syncope associated with tonic-clonic seizures and other epileptic seizures may occur after vaccination. Syncope related to tonic-clonic seizures is usually transient and typically responds to restoring cerebral perfusion by keeping a supine or Trendelenburg position. Some individuals may experience psychogenic reactions before or after the vaccination, and measures should be taken to avoid the injury from the syncope.

5.Like other vaccines for injection, the vaccination of WALRINVAX® should be postponed for individuals 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. Only low-grade fever and mild upper respiratory tract infection are not absolute contraindications to vaccination.

6.WALRINVAX® should be used with caution in individuals with thrombocytopenia or any coagulation disorder.

7.Like any other vaccine, vaccination with WALRINVAX® may not result in protective effect for all vaccinees.

8.WALRINVAX® is only used for preventive purposes, but not indicated for the treatment of exiting HPV-related lesions or prevent their progression of lesions.

9.WALRINVAX® cannot prevent all lesions induced by high-risk HPV infections. WALRINVAX® has not been proved to prevent lesions and diseases caused by infection of HPV types not included in the vaccine.

10.There has been no data on the use of the vaccine in immunocompromised individuals (such as using immunosuppressive drugs). Like other vaccines, WALRINVAX® may not induce an adequate immune response in immunocompromised individuals.

11.The duration of protection of following a complete schedule of immunization with WALRINVAX® has not been fully established. In the phase Ⅲ clinical trial, the protective efficacy of WALRINVAX® on CIN2/3 and AIS was followed-up to 48 months after the first dose (median: 48.3 months); in the phase Ⅱ clinical trial, the immune persistence study in 9 through 17 years of age followed up to 48 months after the first dose (median: 48.0 months) (see [Clinical Trials] for details).

【Pregnant and Nursing Women】

Pregnant Women

1.At present, no independent studies have been conducted to systematically evaluate the effects of WALRINVAX ®on pregnant women. In clinical trials, a total of 212 unintended pregnancy were collected after WALRINVAX® vaccination. Though the clinical trials have revealed no evidence of adverse effects of WALRINVAX® on pregnancy outcomes and neonatal health status, the available data are insufficient to inform vaccine-associated risks in pregnancy.

2.Animal experiments have shown no direct or indirect adverse effects on reproduction, pregnancy, embryo/fetal development, delivery or postnatal development due to WALRINVAX®.

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3.Vaccination of WALRINVAX® should be avoided during pregnancy. Individuals who are trying or are pregnant shall be instructed to defer vaccination until the end of their pregnancy.

Nursing Women

There has been no data when WALRINVAX® is administered to nursing women. As many drugs can be excreted in human milk, WALRINVAX® should be used with caution in nursing women.

【Drug Interaction】

1.The use of immunoglobulins or other blood products should be avoided within 3 months prior to the WALRINVAX®.

2.At present, there is no clinical study on concomitant administration of WALRINVAX® with other vaccines. WALRINVAX® is not recommended to be administrated at the same time with other vaccines.

3.Immunosuppressive medications, including (Immunosuppressive agents, chemotherapy drugs, antimetabolites, alkylating agents, cytotoxin drugs, and corticosteroids, etc.) may reduce the immune response to vaccine.

4.There is no clinical evidence to show the impact of hormonal contraceptives on the efficacy of WALRINVAX®.

5.There are no data to support the interchangeable use between WALRINVAX® and other HPV vaccines.

6.For individuals who are using medicinal products, in order to avoid possible drug interactions, it is recommended to consult a professional physician before WALRINVAX® administration.

【Clinical Trials】

A summary of four clinical trials conducted in China is shown in Table 1.

Table 1. Summary of four clinical trials in China

Study No.	Phase	Study design	Study population	Total number of subjects	Number of subjects (Aged 9-30)
311-HPV-1001	Phase I	Randomized, double-blind, placebo-controlled safety and preliminary immunogenicity study	Females 9 through 45 years of age	160	75
311-HPV-1002	Phase II	Randomized, double-blind, placebo-controlled immunogenicity and safety study (including immune persistence)	Females 9 through 45 years of age	1,200	890
311-HPV-1003	Phase III	Randomized, double-blind, placebo-controlled, multi-center efficacy study	Females 18 through 30 years of age	12,000	12000[a]
311-HPV-1004	Phase IIIb	Randomized, controlled immunobridging study	Females 9 through 26 years of age	900	900[b]

[a] Does not include subjects aged 9-17 years, [b] Does not include subjects aged 15-17years or 27-30 years.

1.Prophylactic Efficacy Against HPV Types 16 and 18

Efficacy of WALRINVAX® was assessed in Study 311-HPV-1003 which enrolled 12,000 healthy females 18 through 30 years of age receiving 3 doses of WALRINVAX® or placebo. Final analysis was performed 48 months after the first dose (median 48.3 months). The efficacy against histopathologically confirmed CIN2+ lesions (CIN 2/3, AIS or Cervical Cancer) associated with HPV-16 and / or -18 infection in the per-protocol set (PPS-1) population is shown in Table 2.

Table 2. Analysis of efficacy of WALRINVAX® in prevention of HPV16 and /or 18-related CIN2+ lesions in females 18 through 30 years of age (PPS-1)

Disease Endpoint	WALRINVAX®		Placebo		% Efficacy (95% CI)
	Number of subjects	Number of cases	Number of subjects	Number of cases	
CIN2/3, AIS and cervical cancer associated to HPV 16 and/or HPV18	5190	3	5167	14	78.59（23.29, 96.06）

The PPS-1 population consisted of individuals who received 3 doses of vaccine according to the study protocol, and were with normal cytology or low-grade lesions, and naïve (PCR negative and seronegative) to the relevant HPV type(s) at Month 0 and Month 6. Efficacy was measured starting after completion of 3 dose vaccinations.

2. Immunogenicity

（1）Immune response of females 9 to 30 years of age receiving 3-dose schedule

A summary analysis of three clinical studies (311-HPV-1002, 311-HPV-1003, and 311-HPV-1004) showed above 99.77% of subjects who received WALRINVAX® became seropositive for antibodies against vaccine type(s) by Month 7(one month post dose 3) across all groups tested. GMTs were higher in 9- through 17-year-old girls than in 18- through 30-year-old women (Table 3).

Table 3. Summary of immunogenicity in girls 9 through17 years of age and women 18 through 30 years of age (PPS)

Group	Number of subjects	Number of seropositive subjects	Positive rate (95% CI)	GMT (95% CI)
Anti- HPV 16				
9- to 17-year-old girls	553	552	99.82 (99.00, 100.00)	7373.58 (6763.35, 8038.86)
18- to 30-year-old women	827	826	99.88 (99.33, 100.00)	3843.98 (3581.81, 4125.34)
Anti- HPV 18				
9- to 17-year-old girls	553	552	99.82 (99.00, 100.00)	6628.38 (6006.61, 7314.53)
18- to 30-year-old women	854	852	99.77 (99.16, 99.97)	2595.57 (2397.78, 2809.68)

PPS population consisted of individuals who received 3 doses of vaccination and were seronegative to the relative HPV type(s) prior to dose 1. Pseudovirus based neutralization assay (PBNA) was used for antibody testing; The positive cutoff value of neutralizing antibodies against HPV 16 and HPV 18 was 1:40.

（2）Immune response in girls 9 through 14 years of age using 2-dose schedule

In the immunobridging study (311-HPV-1004), the neutralizing antibody GMT and seropositivity rate in girls 9 through 14 years of age receiving a 2-dose regimen were non-inferior to those observed in females 18 through 26 years of age receiving a 3-dose regimen for both HPV-16 and HPV-18 antigens. Non-inferiority was based on the lower limit of 95% CI for GMT ratio above 0.67, and the lower limit of 95% CI for seropositivity rates above -5% (Table 4).

Table 4. Comparison of GMT and seropositivity rate between girls 9 through 14 years of age and women 18 through 26 years of age(PPS)

Group	Number of subjects	Number of seropositive subjects	Seropositivity rate % (95% CI)	Seropositivity rate difference (95%CI)	GMT (95% CI)	GMT ratio (9-14 yearsold / 18-26 years old (95% CI)
Anti- HPV 16						
Girls 9-14 years (0, 6)†	288	288	100.00 (98.73, 100.00)	0.00	8511.38 (7585.78, 9549.93)	1.62 (1.41, 1.91)
Women 18~26 years (0,2,6)†	267	267	100.00 (98.63, 100.00)	(-1.33, 1.43)	5128.61 (4677.35, 5754.40)	
Anti- HPV 18						
Girls 9-14 years (0, 6)†	288	288	100.00 (98.73, 100.00)	0.00	7079.46 (6309.57, 8128.31)	2.69 (2.19, 3.24)
Women 18~26 years (0,2,6)†	274	274	100.00 (98.66, 100.00)	(-1.33, 1.39)	2691.53 (2344.23, 3090.30)	

PPS population consisted of individuals who received all assigned vaccination and were seronegative to the relative HPV type(s) prior to dose 1. Pseudovirus based neutralization assay (PBNA) was used for antibody testing; The positive cutoff value of neutralizing antibodies against HPV 16 and HPV 18 was 1:40.

† 2-dose regimen(0.6): vaccination at Day 1 and Month 6; 3-dose regimen (0,2,6) : vaccination at Day 1, Month 2, and Month 6.

（3）Persistence of immune response in females 9 through 17 years of age following 3-dose regimen

In the 311-HPV-1002 study, the persistence of immune response was assessed in females 9 through 17 years of age receiving 3 dose of WALRINVAX® (Table 5).

Table 5. Persistence of seropositivity rate and neutralizing antibody GMT among females 9 through 17 years of age (PPS)

Group	Number of subjects	Number of seropositive subjects	Positive rate (95% CI)	GMT (95% CI)
Anti- HPV 16				
Month 7	265	264	99.62 (97.92, 99.99)	8571.45 (7437.30, 9878.50)
Month 12	265	265	100.00 (98.62, 100.00)	1577.93 (1408.00, 1768.40)
Month 24	242	242	100.00 (98.49, 100.00)	1916.92 (1668.50, 2202.40)
Month 36	235	235	100.00 (98.44, 100.00)	1161.28 (1007.80, 1338.10)
Month 48	206	203	98.54 (95.80, 99.70)	762.37 (650.37, 893.66)
Anti- HPV 18				
Month 7	263	262	99.62 (97.90, 99.99)	5825.80 (5087.20, 6671.70)
Month 12	263	262	99.62 (97.90, 99.99)	3111.29 (2687.00, 3602.60)
Month 24	242	241	99.59 (97.72, 99.99)	1371.08 (1168.70, 1608.50)
Month 36	235	235	100.00 (98.44, 100.00)	1069.23 (903.80, 1264.90)
Month 48	206	201	97.57 (94.43, 99.21)	742.13 (625.20, 880.91)

PPS population consisted of individuals who received 3 doses of vaccinations and were seronegative to the relative HPV type(s) prior to dose 1. Pseudovirus based neutralization assay (PBNA) was used for antibody testing; The positive cutoff value of neutralizing antibodies against HPV 16 and HPV 18 is 1:40.

【Storage】

Store at 2℃ to 8℃. Protect from light. Do not freeze. Discard if vaccine has been frozen.

【Packaging】

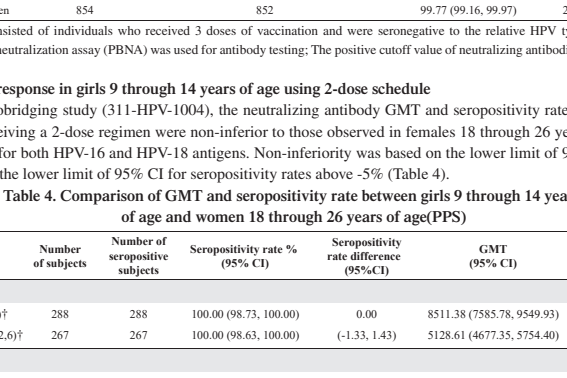
20 Single-dose 0.5 mL Vials.

【Shelf Life】

36 months. Use within the expiry date indicated on the vial or box label.

【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 include in guidance and training materials.



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【Marketing Authorization Holder】

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【Drug Electronic Supervision Code】

Product traceability information can be retrieved by scanning the code on the package.

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