Package Insert

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

Please read the package insert carefully and follow the physician's guidance to use

1 PRODUCT NAME

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

Trade name: WALRINVAX

2 PRODUCT DESCRIPTION

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

Active substances: HPV Type 16 L1 protein and HPV Type 18 L1 protein.

Adjuvant: aluminum phosphate.

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

WALRINVAX is a preservative-free and antibiotic-free vaccine.

3 INDICATION

WALRINVAX is a vaccine for use in females 9 through 30 years of age for the prevention of the following diseases caused by high-risk HPV Types 16, 18 (see Section 14 CLINICAL TRIALS for details):

- Cervical cancer;
- Cervical intraepithelial neoplasia of grade 2 or grade 3 (CIN2/3) and cervical adenocarcinoma *in situ* (AIS).

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.

4 NAME AND STRENGTH OF SUBSTANCES

WALRINVAX is presented as a single-dose of 0.5mL in a vial or pre-filled syringe (PFS) for intramuscular injection only.

Each dose (0.5 mL) contains:

Active ingredients:	
Human Papillomavirus Type 16 L1 protein	40 μg
Human Papillomavirus Type 18 L1 protein	20 μg
Adjuvant:	
Aluminum phosphate (as aluminum)	225 μg
Excipients:	
Sodium chloride	9.35 mg
Histidine	0.7725 mg
Polysorbate 80	0.025 mg
Water for injection	Up to 0.5 mL

5 DOSAGE AND ADMINISTRATION

This product is a milky white suspension, shake vigorously immediately prior to use to obtain a homogeneous milky white suspension. This product is for intramuscular injection only. The preferred site for injection is the deltoid region of the upper arm. The injection volume is 0.5 mL for each single human dose. WALRINVAX should be administrated as soon as possible after being removed from the refrigeration. The need for a booster dose has not been established.

Single-dose Vial Use: Withdraw the 0.5 mL dose of vaccine from the single-dose vial using a sterile needle and syringe and use promptly. A separate needle and syringe should be used for each injection.

Pre-filled Syringe Use: Administer the entire dose as per standard protocol. The single-dose PFS should not be reused.

Vaccination schedules

Age at Dose 1	**Immunization and schedule**
9 through 14 years	2 doses at 0, 6 months[*] 3 doses at 0, 2, 6 months[#]
15 through 30 years	3 doses at 0, 2, 6 months[#]

[*] The interval between the Dose 1 and Dose 2 shall not be less than 5 months.

[#] Dose 2 could be vaccinated within 2 to 3 months after Dose 1, and Dose 3 could be vaccinated within 6 to 7 months after Dose 1.

6 ADVERSE REACTIONS

6.1 Clinical Trials of WALRINVAX

The safety of WALRINVAX was assessed in 4 clinical trials (phase I with study No. 311-HPV-1001 study, phase II with study No.311-HPV-1002 study, phase III with study No.311-HPV-1003 study and phase IIIb with study No. 311-HPV-1004 study)[1] conducted in China. A total of 7,371 females 9 through 30 years of age (including 921 females 9 through 17 years of age and 6,450 females 18 through 30 years of age) received at least one dose of WALRINVAX. The following events/reactions were reported: immediate adverse reactions within 30 minutes after each dose, adverse events within 30 days after each dose, and all serious adverse events within 48

[1] Studies' Identifier: NTC01548118 for 311-HPV-1001 study; NCT02740790 for 311-HPV-1002 study; NCT02733068 for 311-HPV-1003; NCT02740777 for 311-HPV-1004 study

months after the Dose 1.

6.1.1 Summary

The incidence rates of adverse reactions reported in clinical trials, according to the guidance on classifications of adverse reactions recommended by The Council for International Organizations of Medical Sciences (CIOMS), are classified as: very common (≥ 10%), common (≥ 1% to < 10%), uncommon (≥ 0.1% to < 1%), rare (≥ 0.01% to < 0.1%) and very rare (< 0.01%). The safety data for the WALRINVAX collected from all conducted clinical trials of all subjects are summarized as follows:

Table 6-1 Adverse Reactions Reported in Clinical Trials and Classified by CIOMS

	Systemic Adverse Reactions	Injection Site Adverse Reactions
Very Common (≥ 10%)	Fever	Pain
Common (≥ 1% to < 10%)	Headache Fatigue Nausea Vomiting Myalgia Diarrhea	Pruritus Swelling Erythema Induration
Uncommon (≥ 0.1% to < 1%)	Allergic reaction Menstrual disorder Dizziness	/
Rare (≥ 0.01% to < 0.1%)	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 Erythema Rash Acne Back pain Arthralgia Insomnia Fear of injection Asthenopia	Paraesthesia

6.2 Adverse Reactions Reported in Clinical Trials of Similar Products in China and Abroad

In addition to the above-mentioned adverse reactions, the following adverse reactions have been reported 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.

6.3 Post-marketing Surveillance of Similar Products

According to the post-marketing monitoring of similar products in China and abroad, the following safety data were also reported. Since the safety events were spontaneously reported by uncertainly sized population, accurate estimation of the incidence rates and the causal relationship between AEs and investigational products are difficult to confirm:

Immune system disorders: bronchospasm, angioedema

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

Infections and infestations disorders: cellulitis

Blood and lymphatic system disorders: primary thrombocytopenic purpura

Others: severe symptoms of pain (such as myalgia, arthralgia and skin pain) were not limited to the injection site, numbness and powerlessness may be reported by vaccine recipients. These adverse events may last for a long period without clear pathogenic mechanisms.

7 CONTRAINDICATIONS

1. Individuals who are hypersensitivity to any component of the product, including active substances, excipients, etc.
2. Individuals who develop severe allergic reaction after receiving a dose of WALRINVAX should not receive further dose of WALRINVAX.

8 PRECAUTIONS

1. Vaccination can neither replace routine cervical cancer screening, nor 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 is visible in the vial, and the expiration date is exceeded.
3. As with 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. As with 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. As with any other vaccine, vaccination with WALRINVAX may not result in protective effect for all vaccinees.
8. WALRINVAX is only used for preventive purposes, and is not indicated for the treatment of exiting HPV-related lesions or prevent the 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). As with 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 against 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 subjects 9 through 17 years of age was followed up to 48 months after the first dose (median: 48.0 months) (see CLINICAL TRIALS for details).

9 PREGNANCY AND LACTATION

9.1 Pregnancy

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

Animal

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

Human

At present, no specific studies in pregnant women have been conducted to systematically evaluate the safety and immunogenicity of WALRINVAX. In clinical trials, a total of 212 unexpected pregnancy events were collected after WALRINVAX vaccination. Although no adverse effects of WALRINVAX on pregnancy outcomes and neonatal health status were observed in these clinical trials, the available data are insufficient to inform vaccine-associated risks in pregnancy.

9.2 Lactation

Vaccination of WALRINVAX should be avoided during lactation. Whether this product is excreted into human milk remains unknown.

10 INTERACTION WITH OTHER MEDICAMENTS

10.1 Concomitant Vaccine Administrations

No concomitant immunization data of WALRINVAX are available. WALRINVAX is not recommended to be concomitantly administrated with other vaccines.

10.2 Immunoglobulin or Other Blood Products

The use of immunoglobulin or other blood products should be avoided within 3 months prior to the administration of WALRINVAX.

10.3 Immunosuppressive Therapies

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune responses to WALRINVAX.

10.4 Hormonal Contraceptives

No clinical evidence is available to present the impact of hormonal contraceptives on the efficacy of WALRINVAX.

10.5 Prior Vaccination with Other HPV vaccines

No data are available to support the interchangeable use between WALRINVAX and other HPV vaccines.

11 OVERDOSE AND TREATMENT

Overdose with WALRINVAX is unlikely due to its presentation as a single-dose vial/prefilled syringe. No overdose data are available for the product in recipients.

12 PHARMACODYNAMIC/PHARMACOKINETICS

Not applicable.

13 CLINICAL TRIALS

A summary of four clinical trials of WALRINVAX conducted in China is shown in Table 13-1.

Table 13-1 Summary of Clinical Trials in China

Study No.	Phase	Study Design	Study Population	N*	n#
311-HPV-1001	Phase I	Randomized, double-blind, placebo-controlled study	Females 9 through 45 years of age	160	75
311-HPV-1002	Phase II	Randomized, double-blind, placebo-controlled study	Females 9 through 45 years of age	1,200	890
311-HPV-1003	Phase III	Randomized, double-blind, placebo-controlled, multi-center study	Females 18 through 30 years of age	12,000	12,000[a]
311-HPV-1004	Phase IIIb	Randomized, controlled immunobridging study	Females 9 through 26 years of age	900	900[b]

* The total number of subjects included in each clinical trial

\# The number of subjects 9 through 30 years of age

[a] Subjects aged 9-17 years were not included

[b] Subjects aged 15-17 years or 27-30 years were not included

13.1 Vaccine Efficacy Against HPV Types 16 and 18

Vaccine efficacy of WALRINVAX was assessed in Study 311-HPV-1003. A total of 12,000 healthy females 18 through 30 years of age were enrolled and received 3 doses of WALRINVAX or placebo. Final analysis was performed at 48 months after Dose 1 (median 48.3 months). The efficacy against histopathologically confirmed $CIN2^+$ lesions (CIN 2/3, AIS or cervical cancer) associated with HPV-16 and / or HPV-18 infection in per-protocol set 1 (PPS-1) is shown in Table 13-2.

Table 13-2 Efficacy of WALRINVAX in Prevention of HPV-16 and /or HPV-18-related CIN2$^+$ Lesions in Females 18 through 30 Years of Age (PPS-1)

Disease Endpoint	WALRINVAX		Placebo		% Efficacy (95% CI)
	N*	n#	N*	n#	
CIN2/3, AIS and cervical cancer associated to HPV 16 and/or HPV18	5,190	3	5,167	14	78.59 (23.29, 96.06)

Note:
(1) The PPS-1 consisted of individuals who received 3 doses of investigational product according to the study protocol, and were with normal cytology or low-grade lesions, as well as naïve (PCR negative and seronegative) to the relevant HPV type(s) at Month 0 and Month 6.
(2) Efficacy was measured starting after completion of 3 dose vaccinations.
* The total number of subjects included in each group
# The number of subjects who were diagnosed as CIN2/3, AIS or cervical cancer associated to HPV 16 and/or HPV 18

13.2 Immunogenicity

(1) Immune response in females aged 9-30 years following 3-dose regimen of WALRINVAX

A summary analysis of three clinical studies (311-HPV-1002, 311-HPV-1003, and 311-HPV-1004) showed that above 99.77% of subjects who received WALRINVAX became seropositive for antibodies against HPV-16 and HPV-18 by Month 7 (one month post Dose 3) across all groups. Higher GMTs were noted in females aged 9-17 years as compared to those in females aged 18-30 years. Please refer to Table 13-3 for details.

Table 13-3 Summary of Immunogenicity in Females Aged 9-17 Years and Females Aged 18-30 Years (PPS)

Group	N*	n#	Seropositive Rate (95% CI)	GMT (95% CI)
Anti- HPV 16				
Females aged 9-17 years	553	552	99.82 (99.00, 100.00)	7373.58 (6763.35, 8038.86)
Females aged 18-30 years	827	826	99.88 (99.33, 100.00)	3843.98 (3581.81, 4125.34)
Anti- HPV 18				
Females aged 9-17 years	553	552	99.82 (99.00, 100.00)	6628.38 (6006.61, 7314.53)
Females aged 18-30 years	854	852	99.77 (99.16, 99.97)	2595.57 (2397.78, 2809.68)

Note:
(1) PPS consisted of individuals who received 3-dose series of investigational product and were seronegative to the relative HPV type(s) prior to Dose 1.
(2) Neutralizing antibody against HPV as measured by pseudovirus neutralization assay
(3) The positive cut-off of neutralizing antibodies against HPV 16 and HPV 18 was 1:40
* The total number of subjects included in the analysis
# The number of subjects who were seropositive in antibodies against corresponding HPV types

(2) Immune response in females aged 9-14 years of age following 2-dose regimen of WALRINVAX

In the immunobridging study (311-HPV-1004), the GMTs and seropositive rates of neutralizing antibody in females aged 9-14 years who have received a 2-dose regimen of WALRINVAX were non-inferior to those observed in females aged 18-26 years who have received a 3-dose regimen of WALRINVAX in terms of both HPV-16 and HPV-18 antigens. Non-inferiority was determined based on the lower limit of 95% CI for GMT ratio above 0.67, and the lower limit of 95% CI for seropositive rates above -5%, please refer to Table 13-4 for details.

Table 13-4 Comparison of GMT and Seropositive Rate between Females Aged 9-14 Years and Females Aged 18-26 Years (PPS)

Group (Dosing Regimen)	N*	n#	%& (95% CI)	Rate Difference (95%CI)	GMT (95% CI)	GMT Ratio [a] (95% CI)
Anti-HPV 16						
Females aged 9-14 years (0, 6)	288	288	100.00	0.00	8511.38	1.62

Group (Dosing Regimen)	N*	n#	%& (95% CI)	Rate Difference (95%CI)	GMT (95% CI)	GMT Ratio [a] (95% CI)
			(98.73, 100.0)	(-1.33, 1.43)	(7585.78, 9549.93)	(1.41, 1.91)
Females aged 18-26 years (0,2,6)	267	267	100.00 (98.63, 100.0)		5128.61 (4677.35, 5754.40)	
Anti-HPV 18						
Females aged 9-14 years (0, 6)	288	288	100.00 (98.73, 100.0)	0.00 (-1.33, 1.39)	7079.46 (6309.57, 8128.31)	2.69 (2.19, 3.24)
Females aged 18-26 years (0,2,6)	274	274	100.00 (98.66, 100.0)		2691.53 (2344.23, 3090.30)	

Note:
(1) PPS included individuals who received complete series of investigational product and were seronegative to the relative HPV type(s) prior to Dose 1.
(2) Neutralizing antibody against HPV 16 and HPV 18 as measured by pseudovirus neutralization assay
(3) The positive cut-off of neutralizing antibodies against HPV 16 and HPV 18 was 1:40
* The total number of subjects included in the analysis
[#] The number of subjects who were seropositive in antibodies against corresponding HPV types
[&] "%" refers to the seropositive rate
[a] GMT ration=GMT of females aged 9-14 years/ GMT of females aged 18-26 years

(3) Immune persistence in females aged 9-17 years following 3-dose regimen of WALRINVAX

In the 311-HPV-1002 study, the immune persistence was assessed in females aged 9-17 years following 3-dose series of WALRINVAX, please refer to the Table 13-5 for details.

Table 13-5 The Seropositive Rate and GMT of Neutralizing Antibody among Females aged 9-17 Years for Immune Persistence Evaluation (PPS)

Time Points	N*	n#	%& (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)

Note:
(1) PPS consisted of individuals who received complete series of investigational product and were seronegative to the relative HPV type(s) prior to Dose 1.
(2) Neutralizing antibody against HPV as measured by pseudovirus neutralization assay
(3) The positive cut-off of neutralizing antibodies against HPV 16 and HPV 18 was 1:40
* The total number of subjects included in the analysis
[&] The number of subjects who were seropositive in antibodies against corresponding HPV types
[&] "%" refers to the seropositive rate

14 STORAGE CONDITION

Transport and store refrigerated between 2℃ to 8℃. Protect from light. DO NOT FREEZE. Discard if the vaccine has been frozen. Keep the product in places out of children's reach.

15 DOSAGE FORMS AND PACKAGING AVAILABLE

Vial, 1×0.5 mL single human dose

Pre-filled syringe, 1×0.5 mL single human dose.

16 SHELF LIFE

The shelf life of the vaccine is 24 months. Please use before the expiration date printed on the label or packaging.

17 Approval Number

Approval Number of China: S20220011 (PFS), S20220012 (vial)

18 NAME AND ADDRESS OF MANUFACTURER

Name: Yuxi Zerun Biotechnology Co., Ltd.

Address: No.83 South Dongfeng Road, High-tech Zone, Yuxi, Yunnan Province, P. R. China

Postal code: 653100

Tel: +86 0877-2666261

Fax: +86 0877-2666261

Website: https://en.walvax.com/