Recombinant Hepatitis E Vaccine (*Escherichia coli*)

Package Insert

Please read these instructions carefully and follow the directions of the doctor for use

【Drug Name】Generic name: Recombinant Hepatitis E Vaccine (*Escherichia coli*)

English name: Recombinant Hepatitis E Vaccine

Chinese Phonetic Alphabets: Chongzu Wuxing Ganyan Yimiao (Dachang Aixijun)

【Composition and Description】This product is prepared by purifying, refolding, adding aluminum adjuvant to the hepatitis E virus structural protein expressed in genetically engineered *Escherichia coli* and mixing them together. The product is a white suspension, and may be layering due to precipitate, which can be dispersed on shaking.

Excipients: sodium chloride, disodium hydrogen phosphate, potassium dihydrogen phosphate, potassium chloride, aluminum hydroxide, and water for injection.

This product does not contain preservatives.

【Object of Vaccination】This product is suitable for susceptible population aged 16 years and above. It is recommended for individuals at high risk of hepatitis E virus infection, such as those engaged in animal husbandry or catering, students, military officers and soldiers, women of childbearing age, travelers to endemic areas and so on.

【Indications】After this product is vaccinated, the body can be stimulated to be immune to hepatitis E virus, and this product is used for prevention of hepatitis E.

【Strength】0.5ml per syringe, 1 dose (0.5ml) in human contains 30μg of purified recombinant hepatitis E virus antigen.

【Immunization schedule and Dosage】

(1) Injection site: intramuscular injection at deltoid.

(2) Immunization schedule: 3 doses of intramuscular injection according to Month 0, 1, 6 vaccination regimen, i.e. the first dose is given on the vaccination day, the second dose is given one month after the first dose, and the third dose is given six months after the first dose.

【Adverse reactions】

In Phase I and Phase II clinical studies, a total of 505 volunteers were immunized with hepatitis E vaccine; the incidence of systemic adverse events was 8.5% (109 persons/1279 doses), and the incidence of local adverse events was 7.4% (95 persons/1279 doses); all of the adverse events were mild first-order reactions, and no vaccine-related serious adverse events occurred.

In Phase III clinical trial, safety was evaluated in a total of 112604 healthy volunteers (see details in[Clinical Trial]) : of which 2645 subjects underwent systemic safety observation after each dose of vaccine (on-site observation 30 minutes after each dose, active observation at 6h, 24h, 48h, and 72h, spontaneous reports and weekly follow-up were combined from Day 4 until one month after each vaccination). For the hepatitis E vaccine group, the overall incidence of adverse reactions was 29.79%, and the overall incidence of adverse reactions was 23.85% in hepatitis B vaccine control group, as shown in Table 1; the remaining 109,959 subjects underwent spontaneous reporting-based safety observation (on-site observation 30 minutes after each dose, and spontaneous reporting-based safety observation within one month thereafter). The results showed that the overall incidence of adverse reactions rate was 4.56% in hepatitis E vaccine group, and 3.66% in hepatitis B vaccine control group, as shown in Table 2.

Most adverse events were mild first-order reactions in both test group and control group, and the incidence of the test group was slightly higher than that of the control group. Generally, no special treatment was needed, and the symptoms might alleviate by oneself; when necessary, symptomatic treatment might be given. The difference in local reactions between the two groups were statistically significant, which was possibly

related to different protein content of the two vaccines as analyzed by the investigator. Pain, swelling and itching at the vaccination site were common local reactions; and fever, fatigue, asthenia and headache were common systemic reactions. Women had higher incidence of local and systemic adverse reactions than men. There was no regularity for different age groups, the incidence was relatively low in elderly group aged 61-65 years. No vaccine-related serious adverse reaction was found.

Serious adverse events: within one month after each dose of vaccination, the SAE incidence was 0.44% in test group, and 0.44% in control group. A total of 493 SAE cases were reported, including 22 cases of death (10 cases in test group, and 12 cases in control group) and 471 cases hospitalization for treatment (238 cases in test group, and 233 cases in control group).

According to long-term SAE results observed for subjects 1 month after the 2nd dose and before the 3rd dose as well as within 12 months since 1 month after the 3rd dose, the SAE incidence was 2.53% in test group, and 2.54% in control group. A total of 2,853 cases were reported, including 189 cases of death (95 cases in test group, 94 cases in control group), and 2664 reported cases of hospitalization for treatment (1,328 cases in test group, 1,336 cases in control group). All serious adverse events were confirmed by Data and Safety Monitoring Boards (DSMB) as being unrelated to vaccination.

Table 1 Incidence and Severity of Adverse Reactions under Systemic Observation of Recombinant Hepatitis E Vaccine (*Escherichia coli*)

Division of groups	Hepatitis E Vaccine (30μg) Group	Hepatitis B Vaccine (5μg) Control Group
Number of subjects (n)	1316	1329
Number of subjects experiencing adverse reactions and overall incidence n(%)	392(29.79)	317(23.85)
Grade 1	324(24.62)	275(20.69)
Grade 2	59(4.48)	38(2.86)
Grade 3 and above	9(0.68)	4(0.30)
Number of subjects experiencing local adverse reactions and incidence n(%)	177(13.45)	94(7.07)

Pain	136(10.33)	73(5.49)
Swelling	30(2.28)	8(0.60)
Itching	20(1.52)	13(0.98)
Induration	11(0.84)	5(0.38)
Redness	6 (0.46)	1 (0.08)
Rash	1 (0.08)	2 (0.15)
Others	2 (0.15)	3 (0.23)
Number of subjects experiencing systemic adverse reactions and incidence n(%)	267(20.29)	263(19.79)
Fever	245(18.62)	239(17.98)
Headache	14(1.06)	8(0.60)
Fatigue and asthenia	28(2.13)	20(1.50)
Cough	7 (0.53)	4 (0.30)
Myalgia	6 (0.46)	3 (0.23)
Nausea and vomiting	5 (0.38)	5 (0.38)
Diarrhea	1 (0.08)	1 (0.08)
Allergic reaction	0 (0.00)	4 (0.30)

Please refer to "Guiding Principles for Adverse Reaction Grading Criteria in Clinical Trial of Preventive Vaccine" issued by SFDA for adverse reaction grading criteria.

Table 2 Incidence and Severity of Automatically Reported Adverse Reactions of Recombinant Hepatitis E Vaccine (*Escherichia coli*)

Division of groups	Hepatitis E Vaccine (30μg) Group	Hepatitis B Vaccine (5μg) Control Group
Number of subjects (n)	54986	54973
Number of subjects experiencing adverse reactions and overall incidence n(%)	2507 (4.56)	2011 (3.66)
Grade 1	1821(3.31)	1498(2.72)
Grade 2	566(1.03)	424(0.77)
Grade 3 and above	120(0.22)	89(0.16)
Number of subjects experiencing local adverse reactions and incidence n(%)	1532(2.79)	1051(1.91)
Pain	1143 (2.08)	754 (1.37)
Swelling	455 (0.83)	268 (0.49)
Itching	294 (0.53)	162 (0.29)
Induration	400 (0.73)	230 (0.42)
Redness	427 (0.78)	224 (0.41)
Rash	45 (0.08)	33 (0.06)
Others	7 (0.01)	9 (0.02)

Number of subjects experiencing systemic adverse reactions and incidence n(%)	1068(1.94)	1045(1.90)
Fever	462 (0.84)	476 (0.87)
Headache	241 (0.44)	238 (0.43)
Fatigue and asthenia	182 (0.33)	164 (0.30)
Cough	162 (0.29)	150 (0.27)
Myalgia	99 (0.18)	67 (0.12)
Nausea and vomiting	74 (0.13)	88 (0.16)
Diarrhea	53 (0.10)	70 (0.13)
Allergic reaction	32 (0.06)	17 (0.03)

Please refer to "Guiding Principles for Adverse Reaction Grading Criteria in Clinical Trial of Preventive Vaccine" issued by SFDA for adverse reaction grading criteria.

In case of any adverse reaction not mentioned above, please contact the doctor in time.

【Contraindications】

(1) Anyone who is allergic to any ingredient of the product.

(2) Anyone who has allergy history of any other vaccine.

(3) Anyone who suffers from thrombocytopenia or any other blood coagulation disorder.

(4) Anyone who has history of allergy to kanamycin or other aminoglycoside drug.

(5) Anyone who suffers from acute disease, serious chronic disease, acute onset of chronic disease or fever.

(6) Anyone who has uncontrolled epilepsy or any other progressive nervous system disease.

【Precautions】

(1) Intravenous injection of this product is strictly prohibited!

(2) The product should be used in caution in the following conditions: family or

individual has history of convulsions, suffers from chronic disease, has history of epilepsy, or has allergic constitution.

(3) The appropriate medical treatment such as epinephrine and other drug should always be readily available in the vaccination site in case of rare anaphylactic reactions following the administration of the vaccine. Anyone who is vaccinated should stay in vaccination site for at least 30 minutes' observation after the vaccination.

(4) Any syringes with crack, unclear or invalid label, or vaccine with abnormal appearance should not be used.

(5) The product should be shaken well before injection, and should be used immediately after being opened.

(6) For anyone who has received injection of immunoglobulin, at least more than one month should have passed before inoculation of this vaccine, so as not to affect the immune effect.

(7) Freezing of this product is strictly prohibited!

(8) Use for special population:

Pregnant women: No relevant research data is available for such population, and the advantages and disadvantages should be fully considered before deciding whether to use this product.

Lactating women: No relevant research data is available for such population, and the advantages and disadvantages should be fully considered before deciding whether to use this product.

(9) Drug interactions:

Use with Other Vaccines: No clinical study concerning the impact of concomitant administration of other vaccine on immunogenicity of this product

has been carried out. Currently, there is no available data that can be used to evaluate the impact of concurrent administration of this product with any other vaccine.

Immunosuppressive drugs: These include immunosuppressives, chemotherapy drugs, antimetabolites, alkylating agents, cytotoxic drugs, corticosteroid drugs which may reduce immune response of the body to this product.

Patients undergoing treatment: To avoid possible drug interactions, it is recommended to consult the physician.

【Clinical Trials】

Phase I/II clinical trial: 612 healthy volunteers whose serum antibodies to HEV tested negative, and complied with inclusion / exclusion criteria, were enrolled. 457 subjects were randomly, equally assigned into three groups: group A received the dosing of 20μg of hepatitis E vaccine at Month 0, 1 and 6, respectively; group B received the dosing of 20μg of hepatitis E vaccine at Month 0 and 6, respectively; group C received the dosing of 5μg of commercial hepatitis B vaccine at Month 0, 1 and 6. The serum of the subjects in three-dose groups and two-dose group was collected at Month 0, 2, 6, 7 13 and at Month 0, 1, 6, 7, 13, respectively. The remaining 155 subjects were divided into four groups in a ratio of 2:2:2:1, and received hepatitis E vaccine at the dose of 10μg, 20μg, 30μg and 40μg at Month 0, 1 and 6, respectively; the serum of the subjects in the four groups was collected at Month 0, 2, 6, 7 and 13, respectively. The results showed that product had good safety, no vaccine-related serious adverse event occurred, and the geometric mean concentration (GMC) of serum antibody increased with the increase of vaccine protein content (10μg to 40μg). The difference in GMC between 10μg group and 20μg, 30μg, 40μg groups was statistically significant, while the difference among 20μg, 30μg, and 40μg groups was not significant. By comprehensive consideration of the safety and immunogenicity factors, the regimen of 30μg at Month 0, 1 and 6 was selected for Phase III clinical trial.

Phase III clinical trial: the study was designed to be randomized, double-blind, and

hepatitis-B-vaccine-controlled (1:1 allocation). The trial site was in Dongtai City, Jiangsu Province. The study was carried out in healthy adults aged over 16 (16-65) years who were inhabitants permanent residents at the trial site. The trial was performed in two stages. In the first stage, the main purpose was to investigate the safety (combination of spontaneous report and periodic follow-up), immunogenicity and durability of immunity (immune persistence); in the second stage, the main purpose is to investigate the preventive efficacy and the safety in the expanded population (spontaneous report) of the vaccine. 112,916 on-site subjects were enrolled and randomized, among which 312 subjects were excluded due to inoculation time being out of the specified time window, non-resident population, and vaccination error during blind data review (no adverse events of above grade 3 or hepatitis E occurred within this group) etc, and the final population for analysis was 112,604. There were 56,302 subjects in both test group and control group. The first stage involved a total of 2,645 subjects (1316 in test group and 1329 in control group), the subjects receiving all the doses accounted for 90.06%, and the second stage involved a total of 109,959 subjects, (54,986 in test group and 54,973 in control group), and the subjects receiving all the doses accounted for 86.37%.

Suspected hepatitis was discovered by the established suspected hepatitis monitoring system. The system consisted of all the community health center, the municipal hospital, and the center for disease control at the trial site. Suspected acute hepatitis cases were confirmed when the patient visited the doctor or when all the subjects performed active follow-ups every 3 months on a regular basis in the first and second stages; for the suspected cases, registration, blood collection, inspection of aminotransferase and initial hepatitis typing were performed, and with an interval of 2-6 weeks, follow-up was performed for blood collection and identity confirmation, the investigator would verify and confirm the suspected case (by fingerprint or photograph) again. Laboratory tests included anti-HEV IgM and anti-HEV IgG detection, HEV RNA detection and anti-HAV IgM detection. The criterion for determining suspected acute hepatitis case was that the subject had hepatitis symptoms asthenia and/or poor appetite for more than

3 days and ALT>= 1.0 time of the upper limit of normal value; the case in which hepatitis E was confirmed as suspected acute hepatitis, had any two of the three indicators below: positive serum antibody to HEV IgM; serum positive for HEV RNA; four-time increase of IgG antibody.

Since it was hard to timely collect the serum samples of the inapparent latent infected subjects with current technical means for the confirmation of acute HEV infection, two methods were applied to evaluate protective efficacy of the vaccine against HEV infection: (1) for subjects with suspected hepatitis whose blood was collected during the follow-up, acute hepatitis E infection was confirmed as suspected acute hepatitis and serum HEV RNA tested positive, and (2) for subjects who were included in the serological follow-up of immunity durability immunogenicity subset, their blood were collected at Month 7, 19 and/or 19, 31, the occurrence of cumulative hepatitis E virus infection was evaluated for those whose serum IgG antibody increased by 4 times and above through comparison of the antibodies before and after the vaccination.

The immunogenicity results were shown in Table 3, preventive efficacy against hepatitis E was shown in Table 4, preventive efficacy against acute hepatitis E virus infection was shown in Table 5, and preventive efficacy against cumulative hepatitis E virus infection was shown in Table 6. These indicated that the preventive efficacy of this vaccine against both acute HEV infection and occurrence of hepatitis E was more than 60%.

Table 3 Seroconversion to Antibody After Immunization with Recombinant Hepatitis E Vaccine (*Escherichia coli*) (Month 0 and 7)

Division of groups		Number of Persons Observed	GMC (WU/ml)		GMI	Number of Seroconversion	Seroconversion Rate % (95%CI)	P value
			Month 0	Month 7				
Seropositive before immunization	Vaccine group	2659	0.54	24.74	46	2590	97.41(96.73-97.98)	<0.0001
	Control group	2626	0.53	0.5	0.94	25	0.95(0.62-1.4)	
Seronegative before	Vaccine group	2908	0.039	14.96	383.5	2904	99.86(99.65-99.96)	<0.0001

immunization	Control group	2972	0.039	0.04	1.09	94	3.16(2.56-3.86)	
Total	Vaccine group	5567	0.14	19.02	139.27	5494	98.69(98.35-98.97)	<0.0001
	Control group	5598	0.13	0.13	1.02	119	2.13(1.76-2.54)	

* GMC: geometric mean concentration; GMI: geometric mean intensity.

Table 4 Analysis of Preventive Efficacy of Recombinant Hepatitis E Vaccine (*Escherichia coli*) against Hepatitis E

Analysis Set	ITT Set (subjects received at least one dose during Month 0-19)		PP Set (subjects received all doses during Month 7-19)	
Division of groups	Hepatitis E Vaccine (30μg) Group	Placebo (5μg Hepatitis B Vaccine) Group	Hepatitis E Vaccine(30μg) Group	Placebo (5μg Hepatitis B Vaccine) Group
Number of persons observed (n)	56302	56302	48693	48663
Number of person-years observed	56104.66	56081.20	48594.64	48555.05
Number of Hepatitis E cases	13	39	9	26
Protective Efficacy (%) (95%CI)	66.67(37.56-82.21)		65.41(26.18 -83.79)	
P value	0.0003		0.0040	

Table 5 Analysis of Preventive Efficacy of Recombinant Hepatitis E Vaccine (*Escherichia coli*) against Acute Hepatitis E Virus Infection

Analysis Set	ITT Set (subjects received at least one dose during Month 0-19)		PP Set (subjects received all doses during Month 7-19)	
Division of groups	Hepatitis E Vaccine(30μg) Group	Placebo (5μg Hepatitis B Vaccine) Group	Hepatitis E Vaccine (30μg) Group	Placebo (5μg Hepatitis B Vaccine) Group
Number of persons observed (n)	56302	56302	48693	48663
Number of acute HEV infection	18	48	11	37

Protective Efficacy (%) (95%CI)	62.50 (35.54-78.18)	70.29 (41.76-84.84)
P value	0.0002	0.0002

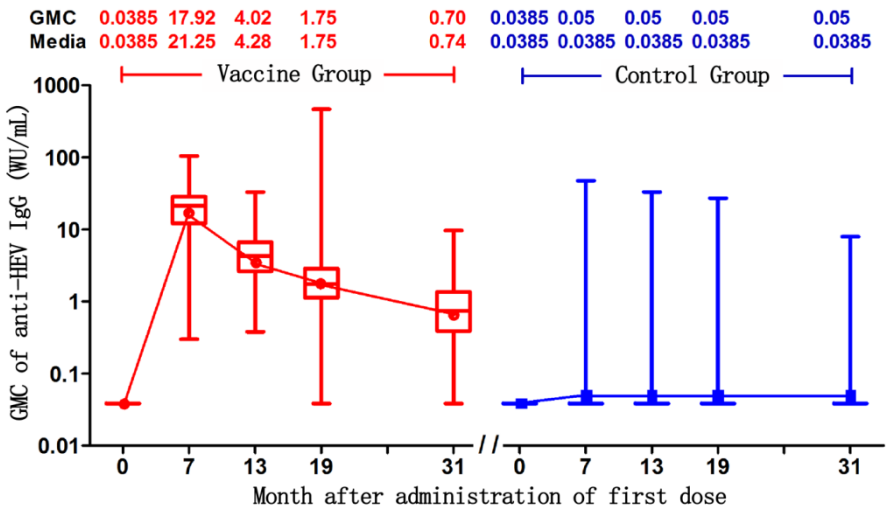
Table 6 Analysis of Preventive Efficacy of Recombinant Hepatitis E Vaccine (*Escherichia coli*) against Cumulative Hepatitis E Virus infection*

Analysis Set	ITT Set (subjects received at least one dose during Month 7-13)*		PP Set (subjects received all doses during Month 7-31)*	
Division of groups	Hepatitis E Vaccine (30μg) Group	Placebo (5μg Hepatitis B Vaccine) Group	Hepatitis E Vaccine (30μg) Group	Placebo(5μg Hepatitis B Vaccine) Group
Seronegative before immunization				
Number of person observed (n)	2187	2183	2075	2079
Number of cumulative infection	17	76	13	72
Incidence of cumulative infections (%)	0.78(0.45-1.25)	3.48(2.74-4.36)	0.63(0.33-1.07)	3.46(2.72-4.34)
Protective Efficacy (%) (95%CI)	77.67(62.23-86.80)		81.91(67.35-89.98)	
P value	<0.0001		<0.0001	
Seropositive before immunization				
Number of person observed (n)	1588	1545	1492	1469
Number of cumulative infection	9	31	9	29
Incidence of cumulative infections (%)	0.57(0.26-1.08)	2.01(1.36-2.85)	0.60(0.28-1.14)	1.97(1.33-2.82)
Protective rate (%) (95%CI)	71.75(40.67-86.55)		68.48(33.42-85.08)	
P value	0.0003		0.0009	
Total				
Number of person observed (n)	3775	3728	3567	3548
Number of cumulative infection	26	107	22	101
Incidence of cumulative infection	0.69(0.45-1.01)	2.87(2.35-3.47)	0.62(0.39-0.93)	2.85(2.32-3.45)

(%)				
Protective rate (%) (95%CI)	76.00(63.17-84.37)		78.33(65.64-86.34)	
P value	<0.0001		<0.0001	

* Those with cumulative infection are defined as those whose IgG antibodies increased by 4 times or more. ITT set is defined as those who received at least one dose, completed baseline antibody test by Month 0, and underwent antibody test at Month 7, 19 and 31. PP set is defined as those who received all the three doses, completed baseline antibody test by Month 0, and underwent antibody test at Month 7, 19 and 31.

Persistence of immune response: The following figure shows dynamic change of the antibody of pre-immunization seronegative subjects after receiving three doses; in the figure, antibody level declined at the fastest rate during Month 7 -13, and at a slower rate during Month 13 -19, and at an even slower rate during Month 19-31. This is similar to dynamic changes of antibodies after inoculation of other vaccines, that is, the antibody reaches a peak after vaccination, it decreases at a fast rate first, and then at a lower speed, and finally stabilizes at a certain level.



In Phase III clinical trial, within the first half year (Month 7-13) after administration of the third dose, serum antibodies of pre-immunization seronegative subjects dropped

from 17.92WU/ml to 4.02WU/ml with average monthly drop rate of 12.7%; during Month 13-19, the serum antibody dropped from 4.02WU/ml to 1.75WU/ml with average monthly drop rate of 4.1%; during Month 19-31, serum antibody dropped from 1.75WU/ml to 0.70WU/ml with average monthly drop rate of 1.2%.

Protective antibody level: The protective antibody level of hepatitis E vaccine remains unknown, and subsequent study is needed after the product is marketed to observe the durability of immunity of the vaccine and evaluate the protective antibody level.

【Storage】Protected from light for storage and transportation at 2 to 8℃. Do not freeze.

【Presentation】1ml pre-filled syringe, one per box. (1 dose (0.5ml) contains 30μg of purified recombinant Hepatitis E Virus Antigen.)

【Shelf life】36 months.

【Executive standard】Implement as per nationally approved registration specification *Procedures for Manufacturing and Verifying Recombinant Hepatitis E Vaccine (Escherichia coli)* (YBS01402011)

【Approval No.】Guo Yao Zhun Zi S20110021

【Marketing Authorization Holder】

Name of manufacture: Xiamen Innovax Biotech Co., Ltd.

Office address: First Floor, No. 50, Shanbianhong East Road, Haicang District, Xiamen City, Fujian Province, China

Post code: 361027

Tel: +86-592-6536555

Fax: +86-592-6536567

Website: http://www.innovax.cn

【Manufacturer】

Name of manufacture: Xiamen Innovax Biotech Co., Ltd.

Address: No.130-1, Xinyuan Road, Haicang District, Xiamen City, Fujian Province, China

Post code: 361022

Tel: +86-592-6536555

Fax: +86-592-6536567

Website: http://www.innovax.cn

Date of verification: 1 Dec 2011

Date of revision: 21 October 2025