Summary of Product Characteristics (SmPC)

Product name: Recombinant Hepatitis E Vaccine (*E. Coli*)

Manufacturer: Xiamen Innovax Biotech Co. Ltd.

Marketer/Importer: Urihk Pharmaceutical Private Limited.

602-603, Sai Samarth Business Park, Near Wasan Motors, Deonar Village Road, Deonar, Govandi (East), Mumbai.

Annexure C to Module I

1．NAME OF THE MEDICINAL PRODUCT

Recombinant Hepatitis E Vaccine (*E. Coli*).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

All components of the drug product are listed as follows:

	Ingredient	**Function**	**Content (for Each Dose)**
Active ingredient	Recombinant HEV 239 protein	Active ingredient	0.030mg
Inactive ingredient	Aluminum hydroxide	Adjuvant	0.800 mg
	Sodium chloride	Osmolality regulator	4.250 mg
	Thiomersal	Preservative	0.025mg
	Disodium hydrogen phosphate	pH regulator	0.144mg
	Potassium dihydrogen phosphate	pH regulator	0.057mg
	Potassium chloride	Osmolality regulator	0.010mg
	Water for injection	As resolvents	/

3. PHARMACEUTICAL FORM

The Recombinant Hepatitis E Vaccine (*E. Coli*) finished product is white mixed suspension with specification of 0.5ml/dose and is filled in pre-filled syringes.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This vaccine is indicated for active immunization against infection caused by Hepatitis E Virus for age group of 18 years to 65 years.

Objective of Vaccination: This product is suitable for susceptible population aged 18 years to 65 years. 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, travellers to endemic areas and so on.

4.2 Posology and method of administration

The Recombinant Hepatitis E Vaccine (*E. Coli*) is applicable to susceptible population aged 18 years to 65 years. The immunization schedule is 3 doses of intramuscular injection at deltoid according to Month 0, 1, 6 vaccination regimen.

4.3 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.

4.4 Special warnings and precautions for use

(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) This product contains thimerosal, and very few persons with allergic constitution may experience anaphylactic reaction to thimerosal after vaccination.

(8) **Freezing of this product is strictly prohibited!**

4.5 Interaction with other medicinal products and other forms of interaction

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.

4.6 Pregnancy and lactation

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.

4.7 Effects on ability to drive and use machines

No relevant research data is available.

4.8 Undesirable effects

Vaccine safety in Chinese population

In a large-scale, randomized, double-blind, and placebo-controlled Phase III clinical trial in

Dongtai city, Jiangsu province, China, vaccine safety was evaluated in a total of 112,604 healthy volunteers: of which 2,645 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 29.8%, and the overall incidence of adverse reactions was 23.9% in hepatitis B vaccine group, as shown in Table 4.8-1; 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 4.6% in hepatitis E vaccine group, and 3.7% in hepatitis B vaccine group, as shown in Table 4.8-2.

Most adverse events were mild, grade 1 in both hepatitis E vaccine group and hepatitis B vaccine group, and the incidence of the hepatitis E vaccine group was slightly higher than that of the hepatitis B vaccine 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 adverse 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 adverse reactions. Fever, fatigue and asthenia, headache were common systemic adverse reactions. No vaccine-related serious adverse reaction was reported.

Table 4.8-1 Incidence and Severity of Adverse Reactions under Systemic Observation of Recombinant Hepatitis E Vaccine (*E.coli*)

Groups	Hepatitis E Vaccine Group	Hepatitis B Vaccine Group
Number of subjects (n)	1316	1329
Number of subjects experiencing adverse reactions and overall incidence n(%)	392(29.8)	317(23.9)
Grade 1	324(24.6)	275(20.7)
Grade 2	59(4.5)	38(2.9)
Grade 3 and above	9(0.7)	4(0.3)
Number of subjects experiencing local adverse reactions and incidence n(%)	177(13.4)	94(7.1)
Pain	136(10.3)	73(5.5)
Swelling	30(2.3)	8(0.6)
Itching	20(1.5)	13(1.0)
Induration	11(0.8)	5(0.4)
Redness	6 (0.5)	1 (0.1)
Rash	1 (0.1)	2 (0.2)
Others	2 (0.2)	3 (0.2)
Number of subjects experiencing systemic adverse reactions and incidence n(%)	267(20.3)	263(19.8)
Fever	245(18.6)	239(18.0)

Groups	Hepatitis E Vaccine Group	Hepatitis B Vaccine Group
Headache	14(1.1)	8(0.6)
Fatigue and asthenia	28(2.1)	20(1.5)
Cough	7 (0.5)	4 (0.3)
Myalgia	6 (0.5)	3 (0.2)
Nausea and vomiting	5 (0.4)	5 (0.4)
Diarrhea	1 (0.1)	1 (0.1)
Allergic reaction	0 (0.0)	4 (0.3)

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 4.8-2 Incidence and Severity of Spontaneous Reported Adverse Reactions of Recombinant Hepatitis E Vaccine (*E.coli*)

Groups	Hepatitis E Vaccine Group	Hepatitis B Vaccine Group
Number of subjects (n)	54986	54973
Number of subjects experiencing adverse reactions and overall incidence n(%)	2507 (4.6)	2011 (3.7)
Grade 1	1821(3.3)	1498(2.7)
Grade 2	566(1.0)	424(0.8)
Grade 3 and above	120(0.2)	89(0.2)
Number of subjects experiencing local adverse reactions and incidence n(%)	1532(2.8)	1051(1.9)
Pain	1143 (2.1)	754 (1.4)
Swelling	455 (0.8)	268 (0.5)
Itching	294 (0.5)	162 (0.3)
Induration	400 (0.7)	230 (0.4)
Redness	427 (0.8)	224 (0.4)
Rash	45 (0.1)	33 (0.1)
Others	7 (0.0)	9 (0.0)
Number of subjects experiencing systemic adverse reactions and incidence n(%)	1068(1.9)	1045(1.9)
Fever	462 (0.8)	476 (0.9)
Headache	241 (0.4)	238 (0.4)
Fatigue and asthenia	182 (0.3)	164 (0.3)
Cough	162 (0.3)	150 (0.3)
Myalgia	99 (0.2)	67 (0.1)
Nausea and vomiting	74 (0.1)	88 (0.2)
Diarrhea	53 (0.1)	70 (0.1)
Allergic reaction	32 (0.1)	17 (0.0)

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

Vaccine safety in Indian population

A multicenter, prospective, randomized, double-blind, placebo-controlled phase III study was conducted in India to evaluate the immunogenicity and safety of hepatitis E vaccine in health adults and adolescents aged 16-65 years.

A total of 190 subjects who met the inclusion and not met the exclusion criteria were randomized to receive either the hepatitis E vaccine or a matching placebo in 1:1 proportion. Subjects were administered 3 doses of vaccine at 0-, 1- & 6-month time points. Each dose was administered intramuscularly over the deltoid.

A total of 17 adverse events in hepatitis E vaccine group, as shown in Table 4.8-3. Most common AE was headache followed by pyrexia. Most subjects have recovered without sequalae. No serious adverse events were reported. No clinical signification during vitals measurement and general examination. No clinically significant findings in the laboratory reports.

Table 4.8-3 Overview of Adverse Events (Safety Population)

	Hepatitis E Vaccine Group (N=97)	Placebo Group (N=93)
	(E)*	(E)*
Overall number of AEs	17	12
Gastrointestinal disorders		
Nausea	1	0
Vomiting	1	0
General disorders and administration site conditions		
Fatigue	1	2
Injection site oedema	1	1
Pain	0	1
Pyrexia	3	0
Musculoskeletal and connective tissue disorders		
Pain in extremity	0	1
Nervous system disorders		
Dizziness	2	0
Headache	6	1
Respiratory, thoracic, and mediastinal disorders		
Nasopharyngitis	0	1
Skin and subcutaneous tissue disorders		
Dry skin	1	0
Pruritus	0	1
Skin and subcutaneous disorder		
Erythema	1	1
Blood and lymphatic system disorders		
Eosinophilia	0	3

*(E) was number of adverse events.

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

4.9 Overdose

There is no overdose in the manufacture of the drug product. An overfill is provided to ensure that a minimum recoverable volume of 0.5 mL/dose is achieved.

5. PHARMACOLOGICAL PROPERTIES

Mechanism of Action

The vaccine produces a specific immune response to the HEV and thus prevents HEV infection, or rapidly clears the virus after infection, thereby achieving the prevention of Hepatitis E

5.1 Pharmacodynamic properties

Efficacy and immunogenicity evaluation in Chinese population

Vaccine efficacy was evaluated in a randomized, double-blind, placebo-controlled, phase III clinical trial in China. A total of 112,604 healthy adults aged 16-65 years were enrolled, and randomly assigned in a 1:1 ratio to receive three doses of hepatitis E vaccine or hepatitis B vaccine intramuscularly at month 0, month 1, and month 6. Participants were followed up for 19 months. The primary endpoint was prevention of hepatitis E during 12 months from the one month after the third dose. Analysis was based on participants who received all three doses per protocol. The vaccine efficacy against Hepatitis E after three doses was 100.0% (95% CI 72.1-100.0) (Table 5.1-1).

Long-term efficacy were evaluated at 4.5 years (month 54) and 10 years (month 120) follow-up of the Phase III clinical trial. The three-dose regimen of hepatitis E vaccine still provided an efficacy of 86.6% (95%CI: 73.0-94.1) over 10 years (Table 5.1-2).

The immunogenicity of hepatitis E vaccine was assessed in 11,165 subjects with three-dose regimen. Serum samples were taken before the first vaccine dose and 1 month after the third dose (month 0 and 7). As shown in Table 5.1-3, 5,494 of 5,567 (98.7%) participants were seroconverted in the hepatitis E vaccine group at month 7. The immunogenicity persistence was assessed at month 55 and month 103. As shown in Table 5.1-4, 87.0% seronegative subjects at baseline still maintained detectable concentrations of antibodies at month 103.

Table 5.1-1 Efficacy of Recombinant Hepatitis E Vaccine (*E. coli*) against Hepatitis E

	Hepatitis E vaccine Group		Hepatitis B vaccine Group		Vaccine efficacy, % (95% CI)
	Number of hepatitis E cases***	Incidence (per 10000 person years)	Number of hepatitis E cases***	Incidence (per 10000 person years)	
ITT Set*					
Month 0-19	1	0.1	22	2.5	95.5 (66.3-99.4)
PP Set**					
Month 7-19	0	0.0	15	3.1	100.0 (72.1-100.0)

*ITT Set: included data collected from baseline among participants who received at least one dose of vaccine.

[**]PP set: included data collected from 1 month after the last vaccination (month 7) among participants who received three doses of vaccine

[***]The definition of hepatitis E cases: acute illness lasting for at least 3 days; abnormal serum ALT concentration 2·5-times the upper limit of normal range or greater; and positive hepatitis E virus IgM and RNA, ≥4-times increase in hepatitis E virus IgG, or both.

Table 5.1-2 Long-term Efficacy of Recombinant Hepatitis E Vaccine (*E. coli*) against Hepatitis E

	Hepatitis E vaccine Group		Hepatitis B vaccine Group		Vaccine efficacy, % (95% CI)
	Number of hepatitis E cases[***]	Incidence (per 10000 person years)	Number of hepatitis E cases[***]	Incidence (per 10000 person years)	
ITT Set[*]					
Month 0-54	7	0.3	53	2.1	86.8 (71.0-94.0)
Month 0-120	13	0.2	77	1.4	83.1 (69.4-91.4)
PP Set[**]					
Month 7-54	3	0.2	45	2.3	93.3 (78.6-97.9)
Month 7-120	9	0.2	67	1.5	86.6 (73.0-94.1)

[*]ITT Set: included data collected from baseline among participants who received at least one dose of vaccine.

[**]PP set: included data collected from 1 month after the last vaccination (month 7) among participants who received three doses of vaccine

[***]The definition of hepatitis E cases: acute illness lasting for at least 3 days; abnormal serum ALT concentration 2·5-times the upper limit of normal range or greater; and positive hepatitis E virus IgM and RNA, ≥4-times increase in hepatitis E virus IgG, or both.

Table 5.1-3 Immunogenicity of Recombinant Hepatitis E Vaccine (*E. coli*) in Chinese Population at Month 7

	Hepatitis E Vaccine Group	Hepatitis B Vaccine Group	P value
Seropositive before immunization			
Number of Persons Observed	2659	2626	-
GMC, WU/ml (95%CI)	24.7 (24.2-25.3)	0.5 (0.5-0.5)	<0.001
Seroconversion rate, % (95%CI)	97.4 (96.7-98.0)	1.0 (0.6-1.4)	<0.001
Seronegative before immunization			
Number of Persons Observed	2908	2972	-
GMC, WU/ml (95%CI)	15.0 (14.5-15.5)	0.0 (0.0-0.0)	<0.001
Seroconversion rate, % (95%CI)	99.9 (99.7-100.0)	3.2 (2.6-3.9)	<0.001
Total			
Number of Persons Observed	5567	5598	-
GMC, WU/ml (95%CI)	19.0 (18.6-19.4)	0.1 (0.1-0.1)	<0.001

Seroconversion rate, % (95%CI)	98.7 (98.4-99.0)	2.1 (1.8-2.5)	<0.001

GMC = geometric mean concentration. GMI = geometric mean increase. WU = WHO units, concentrations of anti-HEV IgG were further determined in parallel with WHO reference reagent (NIBSC code 95/584) and expressed in WHO unit.

Table 5.1-4 Immunogenicity Persistence of Recombinant Hepatitis E Vaccine (*E. coli*) in Chinese Population at Month 55 and Month 103

	Hepatitis E vaccine Group		Hepatitis B vaccine Group	
	Seropositive rate (%) (n/N)	GMC (WU/ml) 95%CI	Seropositive rate (%) (n/N)	GMC (WU/ml) 95%CI
Seropositive before immunization				
Month 55	99.8 (504/505)	2.3 (2.1, 2.4)	89.1 (466/523)	0.3 (0.3, 0.3)
Month 103	100.0 (471/471)	2.6 (2.4, 2.8)	89.4 (470/526)	0.2(0.2, 0.3)
Seronegative before immunization				
Month 55	87.0 (274/315)	0.3 (0.2, 0.3)	8.6 (29/338)	0.0 (0.0, 0.1)
Month 103	87.3 (254/291)	0.2 (0.2, 0.2)	11.7 (39/333)	0.1 (0.0, 0.1)

GMC = geometric mean concentration. WU = WHO units, concentrations of anti-HEV IgG were further determined in parallel with WHO reference reagent (NIBSC code 95/584) and expressed in WHO unit.

Immunogenicity evaluation in Indian population

The immunogenicity of hepatitis E vaccine was evaluated in a randomized, double-blind, placebo-controlled phase III clinical trial in healthy Indian adults and adolescents aged 16-65 years who are seronegative for anti-HEV antibody. The primary endpoint was seroconversion rate from baseline to 1 month after the third dose of hepatitis E vaccine administration in PP Set.

A total of 190 subjects were enrolled, 97 subjects were assigned to the hepatitis E vaccine group and 93 were assigned to the placebo group. In PP set, 88.9% subjects were seroconverted in the hepatitis E vaccine group, which was significantly higher than that in the placebo group (22.4%, P value <0.001) (Table 5.1-5).

Table 5.1-5 Immunogenicity of Recombinant Hepatitis E Vaccine (*E. coli*) in Indian Population at Month 7（PP Set*）

	Hepatitis E Vaccine Group	Placebo Group	P value
Number of Persons Observed	81	76	-
Seroconversion rate, % (95%CI)	88.9 (81.8-96.0)	22.4 (13.0-31.7)	<0.001

*PP set includes subjects without any major protocol violation, who have good dosage compliance, who did not take any prohibited medications during the study period and whose case report form was complete as requested.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Pre-clinical toxicology studies including acute toxicity, repetitive injection immune toxicity, teratogenic toxicity, intramuscular irritation and systemic anaphylaxis were conducted in animals for the recombinant hepatitis E vaccine, as shown in Table 5.3

Table 5.3 Tabulated summary of all toxicology studies

Study	Species	Gender and No. Per group	Groups	Administration Route	Doses	Noteworthy findings
Single-dose Toxicity	KM mice	10 females and 10 males per group	Vaccine test group Diluent control group	Intramuscular injection	16 μg/mouse	No abnormal changes in mice after intramuscular injection with the test vaccine, indicating the vaccine was well tolerated. The maximum tolerated dose (MTD) for female and male mice is > 816.3 μg/kg and >740.7 μg/kg, respectively.
Repeat-dose Toxicity	SD rats	24 males and 24 females per group	Vaccine test group; Negative control; Adjuvant control group	Intramuscular injection	5 μg/rat, 10 μg/rat, 20 μg/rat, 30 μg/rat	No toxicological adverse changes in physical signs, body weight gain, food consumption, haematology, serum biochemistry, urinalysis, or histopathology anatomy of test animals. The NOAEL > 30 μg per rat.
Reproductive and developmental toxicity	SD rats	28 males per group, 56 females per group	Negative control; Vaccine test group	Intramuscular injection	90 μg/rat	No adverse effects were noted on the male and female fertility, the pregnant/lactating female animals, development and growth of the embryos/fetuses, and the F1 pups, and no teratogenic toxicity was noted.

Study	Species	Gender and No. Per group	Groups	Administration Route	Doses	Noteworthy findings
Muscular Irritation Test	Rabbits	1 female and 1 male per group	Diluent control group; Vaccine test group	Intramuscular injection	0.93 μg/kg	No adverse reaction was found in injection sites of test animals.
Systemic Anaphylaxis Test	Guinea Pig	6 animals per group (male and female)	Vaccine test group; Positive control group; Diluent control group;	Test group: Intramuscular injection; Positive and diluent group: intraperitoneal injection	1.65 μg/m2	No anaphylaxis reaction was found in test animals

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients	Quantity (per 500ml of drug product)	Characteristics
Aluminum hydroxide	0.80g	As adjuvant
Sodium chloride	4.25g	As tonicity agents
Thimerosal	25mg	As preservative
Disodium hydrogen phosphate	144mg	As buffering agents
Potassium dihydrogen phosphate	57mg	As buffering agents
Potassium chloride	10mg	As tonicity agents
Water for injection	/	As solvents

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

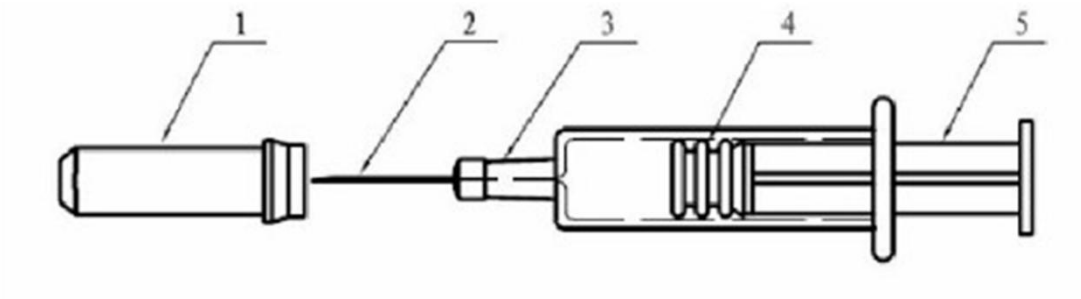
6.4 Special precautions for storage

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

6.5 Nature and contents of container

The filling container for the recombinant hepatitis E vaccine (*E. coli*) product is pre-filled syringe of standard specification (1ml), with filling volume of 0.6ml.

Pre-filled syringe is composed of glass needle tube, piston, needle cap, push rod and syringe needle. Refer to the following figure:



1. Syringe needle protective cap; 2.Syringe needle; 3. Glass needle tube; 4. Rubber piston;5. Push rod

The physic liquor is directly filled into the needle tube and sealed by the piston for storage. When it is to be used, push the push rod.

Description of materials of syringe components

No.	Syringe Assembly	Material
1	Syringe needle protective cap	Polyisoprene rubber
2	Syringe needle	AISI 304 SS

3	Glass needle tube	Middle borosilicate glass
4	Rubber piston	Brominated butyl rubber
5	Push rod	PS

When purchasing filling container (pre-filled syringe) for the product, except for requiring manufacturer to offer certificate of analysis, our company has compiled the specifications and acceptance criteria for factory test according to *Assembly of Standards for Packaging Materials and Containers Directing Contacting the Drugs by CFDA* (2015 Edition), specifications of pre-filled syringe assembly of Becton Dickinson and Company.

6.6 Special precautions for disposal
No special requirements.

7. MARKETING AUTHORISATION HOLDER
Name: Urihk Pharmaceutical Private Limited,
Registered Office address: 602-603, Sai Samarth Business Park, Near Wasan Motors, Deonar Village Road, Deonar, Govandi (East), Mumbai-400088.
Tel: +91-9833637716
E-mail: regulatory@urihkpharma.com

8. MARKETING AUTHORISATION NUMBER(S)
The marketing authorisation number of Recombinant Hepatitis E Vaccine (*E. Coli*) is IMP/BIO/24/000060