Summary of Product Characteristic

1 Name of the Medicinal Product

Generic Name: Recombinant Hepatitis E Vaccine (*Escherichia coli*)

Trade Name: Hecolin™

2 Qualitative and Quantitative Composition

Each dose (0.5mL) contains: Recombinant Hepatitis E antigen 0.030mg

For the full list of excipients, see section 6.1.

3 Pharmaceutical Form

Hecolin™ is presented as 0.5 mL suspension for injection in a pre-filled syringes (PFS).

Upon storage, a fine white deposit with a clear colourless supernatant can be observed. Would be a suspension after thorough agitation.

4 Clinical Particulars

4.1 Therapeutic indication

Recombinant Hepatitis E Vaccine (*Escherichia coli*)/Hecolin™ is used for the prevention of hepatitis E virus infection in individuals ≥ 16 years.

4.2 Posology and method of administration

Posology

Each single-dose PFS contains 0.030mg (0.060mg/mL) of the recombinant hepatitis E antigen in a sterile 0.5 mL volume for intramuscular (IM) injection. The vaccine is administered using a 3-dose schedule (0.030mg/0.5 mL each) at 0, 1 and 6 months.

Method of administration

Hecolin™ is injected intramuscularly and the preferred site for vaccination is deltoid muscle of upper arm. The product is a white suspension, and may be layering due to precipitate, which can be dispersed on shaking.

4.3 Contraindication

(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 drugs.

(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 Warning and Precaution 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

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 immunosupressant, 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 Effect on ability to drive and machine

No relevant research data is available.

4.8 Undesirable effects

a. Summary of the safety profile

In Phase I and Phase II clinical studies, a total of 505 volunteers were immunized in 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: 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; 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.

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.

b. Tabulated list of adverse reactions

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

Test group	Hepatitis E Vaccine (30μg) Group
Number of subjects (n)	1316
Number of subjects experiencing adverse reactions and overall incidence n (%)	392(29.79)
Grade 1	324(24.62)
Grade 2	59(4.48)

Grade 3 and above	9(0.68)
Number of subjects experiencing local adverse reactions and incidence n (%)	177(13.45)
Pain	136(10.33)
Swelling	30(2.28)
Itching	20(1.52)
Induration	11(0.84)
Redness	6 (0.46)
Rash	1 (0.08)
Others	2 (0.15)
Number of subjects experiencing systemic adverse reactions and incidence n (%)	267(20.29)
Fever	245(18.62)
Headache	14(1.06)
Fatigue and asthenia	28(2.13)
Cough	7 (0.53)
Myalgia	6 (0.46)
Nausea and vomiting	5 (0.38)
Diarrhea	1 (0.08)
Allergic reaction	0 (0.00)

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*)

Test group	Hepatitis E Vaccine (30μg) Group
Number of subjects (n)	54986
Number of subjects experiencing adverse reactions and overall incidence n (%)	2507 (4.56)
Grade 1	1821(3.31)
Grade 2	566(1.03)
Grade 3 and above	120(0.22)
Number of subjects experiencing local adverse	1532(2.79)

reactions and incidence n (%)	
Pain	1143 (2.08)
Swelling	455 (0.83)
Itching	294 (0.53)
Induration	400 (0.73)
Redness	427 (0.78)
Rash	45 (0.08)
Others	7 (0.01)
Number of subjects experiencing systemic adverse reactions and incidence n (%)	1068(1.94)
Fever	462 (0.84)
Headache	241 (0.44)
Fatigue and asthenia	182 (0.33)
Cough	162 (0.29)
Myalgia	99 (0.18)
Nausea and vomiting	74 (0.13)
Diarrhea	53 (0.10)
Allergic reaction	32 (0.06)

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

c. Other special populations

No relevant research data is available.

In summary, according to the recommendations of the Council for International Organizations of Medical Sciences (CIOMS), adverse reactions considered as being at least possibly related to vaccination should be classified by frequency as follows: very common (≥10%), common(≥1% to <10%), uncommon (≥0.1% to <1%), rare (≥0.01% to <0.1%), very rare (<0.01%). The adverse reactions of Hecolin™ are shown in **Table 3**.

Table 3 The lists of adverse reactions of Recombinant Hepatitis E Vaccine (*Escherichia coli*)

System Organ Class	Frequency	Adverse reactions
Systemic Adverse Reactions		
General disorders	Very common	Fever (≥37.1 ℃)

and administration site conditions	Common	Fatigue
Gastrointestinal disorders	Common	Nausea, vomiting
	Rare	Diarrhea
Nervous system disorders	Common	Headache
Immune system disorders	Uncommon	Hypersensitivity
Respiratory, thoracic and mediastinal disorders	Uncommon	Cough
Musculoskeletal and connective tissue disorders	Uncommon	Muscle pain
Local Adverse Reactions		
General disorders and administration site conditions	Very common	Injection site pain
	Common	Injection site swelling, injection site pruritus
	Uncommon	Injection site induration, injection site erythema, injection site discomfort
	Rare	Injection site rash

Reporting of Adverse Reaction

Healthcare professionals should report suspected adverse reaction of this product via:

Pusat Farmakovigilans/MESO Nasional Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif Badan Pengawas Obat dan Makanan.

Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560

E-mail: pv-center@pom.go.id

Phone: +62-21-4244691 Ext.1079

Website: https://e-meso.pom.go.id/ADR

and

PT. TRIMAN

Jl. Pendeuy Km. 1 Rancaekek, 40394, Indonesia

E-mail: pv@triman.co.id

Phone: +628-1668-1668

4.9 Overdose

There is no data regarding overdose of this vaccine.

5 Pharmaceutical properties

5.1 Pharmacodynamics properties

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$\geqslant$ 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 4**, preventive efficacy against hepatitis E was shown in **Table 5**, preventive efficacy against acute hepatitis E virus infection was shown in **Table 6**, and preventive efficacy against cumulative hepatitis E virus infection was shown in **Table 7**. These indicated that the preventive efficacy of this vaccine against both acute HEV infection and occurrence of hepatitis E was more than 60%.

Table 4 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 immunization	Vaccine group	2908	0.039	14.96	383.5	2904	99.86(99.65-99.96)	<0.0001
	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 5 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 6 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

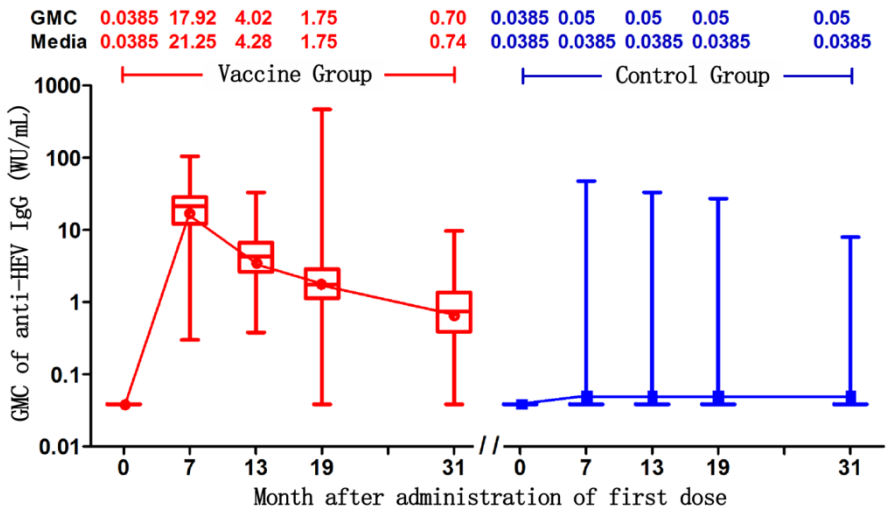
Table 7 Analysis of Preventive Efficacy of Recombinant Hepatitis E Vaccine (*Escherichia coli*) against Cumulative Hepatitis E Virus infection*

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	26	107	22	101

cumulative infection				
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.

5.2 Pharmacokinetics properties

As the product is a prophylactic vaccine derived from a biological (bacterial) source and no novel adjuvant or excipient is included in the product, no specific studies have been performed to assess the PK of the product. As a consequence of traditional PK studies not being relevant, the associated information relating to Absorption, Distribution, Metabolism and Excretion (ADME) is not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on the studies of single-dose and repeated dose toxicity, local tolerance, reproductive and developmental toxicity and systemic anaphylaxis.

6 Pharmaceutical particulars

6.1 List of excipients

Aluminum hydroxide

Sodium chloride

Thimerosal

Disodium hydrogen phosphate dihydrate

Potassium dihydrogen phosphate

Potassium chloride

Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precaution for storage

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

6.5 Nature and content of container

0.5 mL suspension for injection in a pre-filled syringe. Box, 1 syringe @ 0.5 mL.

6.6 Special precautions for disposal and other handling

Not applicable.

7 Manufacturer

Xiamen Innovax Biotech Co., Ltd.

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

8 Imported by

PT. BCHT Bioteknologi Indonesia

Jl. Tanah Abang II No. 67, Jakarta 10160

Indonesia

9 Registration holder

PT. Triman

Jl. Peundeuy Km 1 Rt 02 Rw 11 Desa Bojongsalam Kab. Bandung, Jawa Barat

Indonesia

10 Marketing Authorization Number

XXXXXX

11 Date of first authorization in Indonesia

XXXXXXXXXX

12 Drug Classification

Prescription drugs

HARUS DENGAN RESEP DOKTER

Version 1.0

Front

INFORMASI PRODUK UNTUK PASIEN
HECOLIN

NAMA OBAT
Merk dagang : Hecolin

BENTUK SEDIAAN
Suspensi Injeksi

PEMERIAN OBAT
Suspensi steril berwarna putih yang diisi ke dalam pre-filled syringes (PFS).

Saat disimpan, endapan halus berwarna putih dengan cairan bening tak berwarna dapat diamati. Akan menjadi suspensi setelah diaduk.

KOMPOSISI
ZAT AKTIF
Setiap dosis (0.5 ml) mengandung :
Recombinant Hepatitis E Antigen 0.030 mg

KEKUATAN
30 µg Recombinant Hepatitis E Antigen dalam dosis 0.5 mL.

INDIKASI
Vaksin Hepatitis E Rekombinan (*Escherichia coli*) /Hecolin™ digunakan untuk pencegahan infeksi virus hepatitis E pada individu ≥ 16 tahun.

POSOLOGI DAN CARA PEMBERIAN
Setiap dosis mengandung 30 mcg antigen virus hepatitis E rekombinan dalam volume 0,5 mL steril untuk injeksi intramuskular (IM). Vaksin ini diberikan dengan jadwal 3 dosis masing- masing pada 0, 1, dan 6 bulan.

KONTRAINDIKASI
1. Hipersensitivitas (reaksi alergi) terhadap bahan yang digunakan dalam produk.
2. Memiliki riwayat alergi terhadap vaksin.
3. Individu yang mengidap kekurangan trombosit atau gangguan penggumpalan darah lain.
4. Memiliki riwayat alergi terhadap antibiotik jenis tertentu (kanamycin atau golongan aminoglikosida lain).
5. Individu yang mengidap penyakit akut, kronis serius, kronis akut atau demam.
6. Individu dengan epilepsi tidak terkontrol atau gangguan sistem saraf progresif lain.

PERINGATAN KHUSUS
1. Produk ini dilarang untuk disuntikkan melalui pembuluh darah (intravena).
2. Produk ini harus digunakan secara hati-hati pada kondisi berikut : individu atau keluarga memiliki riwayat kejang, mengidap penyakit kronis, memiliki riwayat epilepsi, atau memiliki kondisi alergi.
3. Obat-obatan seperti epinefrin atau obat lainnya harus selalu tersedia di tempat vaksinasi sebagai penanganan jika terjadi reaksi alergi berat setelah vaksin diberikan. Setelah vaksinasi dilakukan, harap tunggu 30 menit untuk dilakukan pemeriksaan setelah vaksin diberikan.
4. Alat suntik yang rusak, label yang tidak jelas, atau vaksin dengan penampilan yang tidak normal, maka tidak boleh digunakan.
5. Obat harus dikocok terlebih dahulu sebelum injeksi dan harus digunakan segera setelah dibuka.
6. Untuk individu yang telah menerika injeksi imunoglobulin, minimal harus melewati lebih dari 1 bulan sebelum pemberian vaksin ini, agar tidak mempengaruhi efek kekebalan.
7. Produk ini mengandung timerosal, dan terdapat sedikit populasi yang memiliki kondisi alergi yang mungkin mengalami reaksi alergi berat terhadap timerosal setelah vaksinasi.
8. Produk ini dilarang untuk dibekukan!

INTERAKSI OBAT
Penggunaan dengan Vaksin Lain : Tidak ada penelitian mengenai dampak pemberian produk ini bersamaan dengan vaksin atau obat lain.
Obat imunosupresif : Obat penekan sistem kekebalan tubuh dapat mengurangi respon imun terhadap produk ini.
Pasien dalam pengobatan : Untuk menghindari kemungkinan terjadinya interaksi obat, disarankan untuk berkonsultasi dengan dokter.

KEHAMILAN DAN MENYUSUI
Kehamilan : Belum ada data penelitian relevan yang tersedia pada populasi ini, manfaat dan risiko harus dipertimbangkan sebelum memutuskan untuk menggunakan produk ini.
Menyusui : Belum ada data penelitian relevan yang tersedia pada populasi ini, manfaat dan risiko harus dipertimbangkan sebelum memutuskan untuk menggunakan produk ini.

EFEK PADA PENGENDARA DAN MENJALANKAN MESIN
Tidak ada penelitian yang dilakukan.

EFEK SAMPING DAN KEJADIAN IKUTAN PASCA IMUNISASI (KIPI)
Dalam studi klinis Fase I dan Fase II, total 505 sukarelawan diimunisasi hepatitis vaksin E; kejadian efek samping sistemik adalah 8,5% (109 orang/1279 dosis), dan kejadian efek samping lokal adalah 7,4% (95 orang/1279 dosis); KIPI yang muncul adalah reaksi ringan, dan tidak ada efek samping serius terkait vaksin yang terjadi.

Dalam uji klinis Fase III, keamanan dievaluasi pada total 112604 sukarelawan sehat: di antaranya: 2645 subjek menjalani pemeriksaan keamanan secara menyeluruh setelah setiap dosis vaksin (di tempat pengamatan 30 menit setelah setiap dosis, pengamatan aktif pada 6 jam, 24 jam, 48 jam, dan 72 jam, laporan spontan dan tindak lanjut mingguan digabungkan dari Hari 4 sampai satu bulan setelahnya setiap vaksinasi). Untuk kelompok vaksin hepatitis E, insiden keseluruhan KIPI sebesar 29,79%, dan keseluruhan insiden KIPI sebesar 23,85% pada vaksin hepatitis B kelompok kontrol; 109.959 subjek sisanya menjalani pemeriksaan keselamatan berbasis pelaporan spontan (pengamatan di tempat 30 menit setelah setiap dosis dan pemeriksaan keselamatan berbasis pelaporan spontan dalam waktu satu bulan sesudahnya). Hasilnya menunjukkan bahwa insiden keseluruhan tingkat KIPI sebesar 4,56% pada kelompok vaksin hepatitis E, dan 3,66% pada hepatitis B kelompok kontrol vaksin.

Sebagian besar efek samping merupakan efek samping ringan baik di kelompok uji dan kelompok kontrol, dan insiden kelompok uji sedikit lebih tinggi daripada kelompok kontrol. Umumnya tidak perlu perawatan khusus, dan gejalanya mungkin berkurang dengan sendirinya; bila perlu, pengobatan untuk mengurangi gejala dapat diberikan. Perbedaan reaksi lokal antara kedua kelompok secara statistik signifikan, yang mungkin terkait dengan kandungan protein yang berbeda dari kedua vaksin yang dianalisis oleh peneliti. Nyeri, bengkak, dan gatal di area penyuntikkan adalah reaksi lokal yang umum; demam, kelelahan, asthenia dan sakit kepala adalah reaksi sistemik yang umum. Wanita memiliki insiden KIPI lokal dan sistemik yang lebih tinggi daripada laki-laki. Tidak ada keteraturan untuk kelompok usia yang berbeda, kejadiannya relatif rendah kelompok lansia berusia 61-65 tahun. Tidak ada KIPI serius terkait vaksin yang ditemukan.

Efek samping yang serius / Serious Adverse Event (SAE) : dalam waktu satu bulan setelah setiap dosis vaksinasi, insiden SAE terjadi sebanyak 0,44% pada kelompok uji, dan 0,44% pada kelompok kontrol. Sebanyak 493 kasus SAE dilaporkan, termasuk 22 kasus kematian (10 kasus pada kelompok uji, dan 12 kasus pada kelompok kontrol) dan 471 kasus rawat inap untuk pengobatan (238 kasus pada kelompok uji, dan 233 kasus pada kelompok kontrol).

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Menurut hasil SAE jangka panjang yang diamati untuk subjek 1 bulan setelah dosis kedua dan sebelum dosis ketiga serta dalam waktu 12 bulan sejak 1 bulan setelah dosis ketiga, insiden SAE terjadi sebanyak 2,53% pada kelompok uji, dan 2,54% pada kelompok kontrol. Sebanyak 2.853 kasus dilaporkan, termasuk 189 kasus kematian (95 kasus pada kelompok uji, 94 kasus pada kelompok kontrol), dan 2664 kasus yang dilaporkan rawat inap untuk pengobatan (1.328 kasus dalam kelompok uji, 1.336 kasus di kelompok kontrol). Semua efek samping yang serius dikonfirmasi oleh Data and Safety Monitoring Boards (DSMB) dan dinyatakan tidak berkaitan dengan vaksinasi Hecolin™.

Tabel 1 Kejadian dan Keparahan KIPI dengan Observasi Sistemik terhadap Vaksin Hepatitis E Rekombinan (*Escherichia coli*)

Kelompok Uji	Kelompok Vaksin Hepatitis E (30 µg)
Jumlah subyek (n)	1316
Jumlah subyek yang mengalami KIPI dan keseluruhan insidensi n (%)	392 (29.79)
Tingkat 1	324 (24.62)
Tingkat 2	59 (4.48)
Tingkat 3 dan seterusnya	9 (0.68)
Jumlah subyek yang mengalami KIPI lokal dan insidensi n (%)	177 (13.45)
Nyeri	136 (10.33)
Bengkak	30 (2.28)
Gatal	20 (1.52)
Indurasi	11 (0.84)
Kemerahan	6 (0.46)
Ruam	1 (0.08)
Lainnya	2 (0.15)
Jumlah subyek yang mengalami KIPI sistemik dan insidensi n (%)	267 (20.29)
Demam	245 (18.62)
Sakit Kepala	14 (1.06)
Kelelahan dan astenia	28 (2.13)
Batuk	7 (0.53)
Myalgia	6 (0.46)
Mual dan muntah	5 (0.38)
Diare	1 (0.08)
Reaksi alergi	0 (0.00)

Mengacu pada “Guiding Principles for Adverse Reaction Grading Criteria in Clinical Trial of Preventive Vaccine” yang diterbitkan SFDA untuk Kriteria Tingkatan KIPI.

Tabel 2 Kejadian dan Keparahan KIPI yang Dilaporkan terhadap Vaksin Hepatitis E Rekombinan (*Escherichia coli*)

Kelompok Uji	Kelompok Vaksin Hepatitis E (30 µg)
Jumlah subyek (n)	54986
Jumlah subyek yang mengalami KIPI dan keseluruhan insidensi n (%)	2507 (4.56)
Tingkat 1	1821 (3.31)
Tingkat 2	566 (1.03)
Tingkat 3 dan seterusnya	120 (0.22)
Jumlah subyek yang mengalami KIPI lokal dan insidensi n (%)	1532 (2.79)
Nyeri	1143 (2.08)
Bengkak	455 (0,83)
Gatal	294 (0,53)
Indurasi	400 (0,73)
Kemerahan	427 (0,78)
Ruam	45 (0,08)
Lainnya	7 (0.01)
Jumlah subyek yang mengalami KIPI sistemik dan insidensi n (%)	1068(1,94)
Demam	462 (0,84)
Sakit Kepala	241 (0.44)
Kelelahan dan astenia	182 (0,33)
Batuk	162 (0,29)
Myalgia	99 (0,18)
Mual dan muntah	74 (0,13)
Diare	53 (0.10)
Reaksi alergi	32 (0,06)

Mengacu pada “Guiding Principles for Adverse Reaction Grading Criteria in Clinical Trial of Preventive Vaccine” yang diterbitkan SFDA untuk Kriteria Tingkatan KIPI.

CARA PENYIMPANAN
Terlindung dari cahaya matahari. Disimpan pada suhu 2°C hingga 8°C. Dilarang dibekukan.

UMUR SIMPAN
36 bulan

KEMASAN
1 mL pre-filled syringe / dus

NOMOR IZIN EDAR

HARUS DENGAN RESEP DOKTER

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Part Description	leaflet/brosur PIL HECOLIN	**Software used**	Adobe Illustrator Version 27.0
Packaging Code	Brosur	**Draft by / Date**	YL / 08 - 12 - 2025
Material	HVS / offset paper 80 gsm	**FONT**	Jenis Font / Size
Dimension	140 mm x 175 mm	**Brand Name :**	- / -
Colour	Black	**Generik Brand Name :**	- / -
Finishing	-	**Komposisi, dll :**	Arial / 6 pt
Coating	-		

DISETUJUI BPOM 12 DESEMBER 2025

EREG10035712200065