Version Number: EntroVac-MY-001

Date of Revision: June , 2026

Package Insert for

EntroVac Suspension for Injection Enterovirus Type 71 Vaccine, Inactivated (Human Diploid Cell) In Vial

and

EntroVac Suspension for Injection Enterovirus Type 71 Vaccine, Inactivated (Human Diploid Cell) In Prefilled Syringe

1. DESCRIPTION

The vaccine is a slight milky-white suspension. Stratified precipitate may form which can be dispersed by shaking.

Pharmaceutical form: Suspension for injection

Active substance: Inactivated Enterovirus Type 71 (EV71) antigen.

Excipients: Aluminum hydroxide, glycine. There is no preservative in this product.

2. INDICATIONS

The vaccine is indicated for children from 6 months to 5 years old for the prevention of hand, foot and mouth disease (HFMD) caused by Enterovirus Type 71 (EV71).

3. STRENGTHS

1 dose (0.5 ml per vial) contains 100U inactivated EV71 antigen.

1 dose (0.5 ml per syringe) contains 100U inactivated EV71 antigen.

4. DOSAGE AND ADMINISTRATION

Dosage:

The primary immunization consists of two doses with an interval of one month, 0.5ml per dose. It has not been determined if a booster dose is required.

Method of Administration:

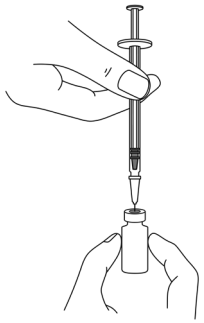
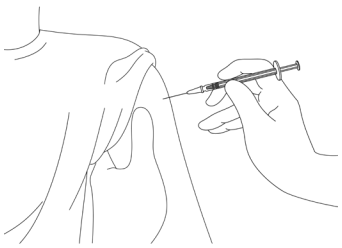
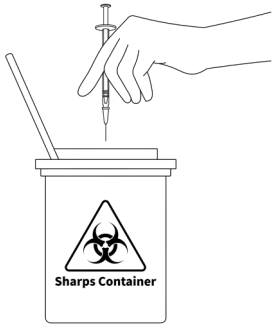
For intramuscular injection only. The preferred injection sites are the deltoid muscle of upper arm or the anterolateral aspect of the thigh, with the appropriate site selected based on the recipient's age and muscle mass or suggestion of healthcare professional.

Instruction for Use:

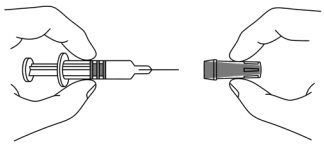
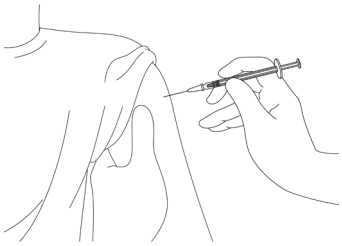
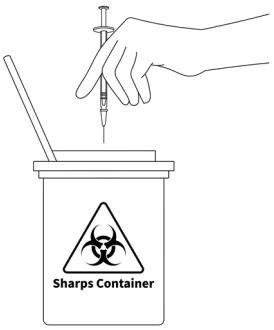
Prior to vaccination, the vaccine should be well shaken in order to obtain a homogeneous turbid white suspension.

Inspect visually prior to administration. Stratified precipitate may form which can be dispersed by shaking. The vaccine should not be used if foreign particles are present in the suspension. The vaccine should be used immediately after opening.

Instruction for Vial:

		
1.Insert the needle of the syringe down into the liquid level of the vial to draw the vaccine.	2.Administer the full dose (0.5 mL) intramuscularly.	3.Discard the syringe to sharps container after a single use.

Instruction for pre-filled syringe (PFS):

		
1.The vaccine in PFS is provided with needle. Remove the needle cap without touching the needle.	2.Administer the full dose (0.5 mL) intramuscularly.	3.Discard the PFS to sharps container after a single use.

Important: Both vial and prefilled syringe presentations are intended for single-dose administration only. Do not store any residual vaccine.

5. CONTRAINDICATIONS

This vaccine is contraindicated to be used in the following situation:

(1) Individuals with known severe allergy to active substances or excipients present.

(2) Individuals with fever or in the period of acute disease.

(3) Individuals with serious chronic disease or with atopy.

6. WARNINGS AND PRECAUTIONS

(1) Do not inject the vaccine intravascularly.

(2) As with all injectable vaccines, appropriate medical treatment (i.e. adrenaline) and supervision should always be readily available in case of a rare anaphylactic event. The recipients shall be observed for at least 30 minutes on site following injection.

(3) The vaccine should be used cautiously in the following situations:

①Individuals with thrombocytopenia or hemorrhagic disease, as intramuscular administration of this vaccine may cause bleeding.

②Individuals receiving immunosuppressive therapy or with immune deficiency disorder, as the immune response to this vaccine may be reduced. Inoculation should be delayed until the end of the treatment or the healthcare professionals considered the benefits of vaccination outweigh the risks. For individuals with chronic immunodeficiency, vaccination is recommended even if the underlying illness may result in limited immune response.

③Individuals with uncontrolled epilepsy and other progressive nervous system disease.

(4) Similar with other vaccines, this vaccine may not elicit 100% efficacy for the vaccine recipients.

(5) This vaccine must be placed out of the reach for children.

(6) Do not use the vaccine if the syringe presents with any abnormality, turbidity or cracks.

(7) Avoid exposure to disinfectants during opening the container and use.

(8) Do not freeze. The vaccine should be used immediately after opening.

(9) The administration of this vaccine should be deferred for at least 1 month following the administration of immunoglobulin to avoid the influence on immune effect.

(10) Limitation of Use: The vaccine cannot be used for the prevention of HFMD caused by other enteroviruses such as Coxsackievirus A16.

7. DRUGS INTERACTIONS

(1) Concomitant administration with other vaccines (*Evaluation of the Immunogenicity and Safety of Enterovirus Type 71 Vaccine, Inactivated (Human Diploid Cell) and Measles and Rubella Vaccine, Live or Japanese Encephalitis Vaccine, Live Simultaneously Inoculated in Infants Aged 8 Months through Randomized and Parallel-Controlled Trial)*: The results showed that the

simultaneous administration of EV71 vaccine with bivalent attenuated Measles and Rubella Vaccine, Live has good immunogenicity and well tolerated.

(2) Immunosuppressive drugs including immune-suppressants, chemotherapy drugs, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroid drugs may reduce the immune response.

(3) Prior to vaccination, patients receiving any form of therapy should consult a healthcare professional to avoid potential drug interactions.

8. PREGNANCY AND LACTATION

Not applicable.

9. ADVERSE REACTIONS

9.1 Clinical Trial Experience

A total of 14,848 participants were involved as subjects for clinical trials, among which 8,572 participants have administrated this vaccine.

Safety surveillance was carried out in the Phase III (*Phase III clinical trial for Enterovirus Type 71 Vaccine, Inactivated*) clinical trial among 12,000 healthy children aged from 6 to 71 months, who were randomized to receive two doses of the vaccine or placebo on day 0 and 28. The incidence of adverse reactions in the vaccine group and the placebo group is 36.58% and 26.40%, respectively, in which the incidence of systemic adverse reactions is 33.75% and 24.92%, respectively. The symptoms include pyrexia, decreased appetite, irritability postvaccinal, diarrhea, nausea, vomiting, fatigue, hypersensitivity, abdominal discomfort, constipation, and oral inflammation. Mild fever is the most common manifestations, but which is transient. As for the local adverse reactions, the incidence is 5.87% and 2.25%, respectively, of which includes pain, erythema, pruritus, swell, and induration on inoculation site. The typical manifestations are local pain and erythema, which lasts no more than 3 days and can be

recovered by its own. There was no intergroup difference (1.18% v.s. 0.93%, p=0.2115) in all symptoms with severity over Grade 3 including pyrexia, irritability, diarrhea, decreased appetite, fatigue, hypersensitivity, pain and erythema, no serious adverse reaction related to the vaccination was observed. All adverse reactions were most apparent at the first dose and no increase in the incidence was seen with subsequent doses.

According to Council for International Organizations of Medical Sciences (CIOMS), the incidence of adverse reactions can be described as follows: very common (≥10%), common (1%-10%，including 1%), uncommon(0.1%-1%，including 0.1%), rare (0.01%-0.1%，including 0.01%), very rare (＜0.01%), all adverse reactions were described as follows:

System Organ Class	**Adverse Reactions**	**Frequency**
General disorders and administration site conditions	Pyrexia	Very common
	Pain, erythema, swelling, induration, fatigue, irritability	Common
	Pruritus	Uncommon
Metabolism and nutrition disorders	Decreased appetite	Common
Gastrointestinal disorders	Diarrhoea, nausea, vomiting	Common
Immune system disorders	Hypersensitivity	Common

9.2 Post-marketing Experience

In addition to the adverse reactions reported in the clinical trials, the following adverse events have been reported after this product has been used on the market. These adverse events are reported from phase IV clinical trials and spontaneous reporting., The frequency of adverse events in post-marketing surveillance and the causal relationship with vaccination is impossible to be established due to the limited reported cases and inconsistent medical judgment.

General disorders and administration site conditions: Irritability.

Respiratory, thoracic and mediastinal disorders: Cough, rhinorrhoea.

Gastrointestinal disorders: Abdominal pain, dyspepsia.

Skin and subcutaneous tissue disorders: Rash, henoch-schonlein purpura (HSP), urticaria, maculo-papular rash.

9.3 Reporting of Adverse Events

Please report any side effects or adverse drug reactions directly to the National Centre for Adverse Drug Reaction Monitoring by visiting the website npra.gov.my [Consumers->Reporting Side Effects to Medicines (ConSERF) or Vaccines (AEFI)].

10. OVERDOSE AND TREATMENT

To date no studies on overdose have been carried out.

11. EFFECT ON ABILITY TO DRIVE AND USE MACHINES

Not applicable since this vaccine is to be used in infants and children only.

12. PHARMACODYNAMICS

12.1 Pharmacotherapeutic Group

The ATC code for enterovirus 71 vaccine is J07BX06

12.2 Mode of action

After inoculation, this vaccine can induce immunity against EV71 to prevent HFMD caused by infection of EV71, including high levels of neutralizing antibodies and activates specific T-cell immunity. The induced neutralizing antibodies primarily targets conformational epitopes on the viral capsid including VP1, VP2 and VP3 to block virus binding to host receptors, preventing

viral internalization, and inducing capsid destabilization and premature genome release, thereby inhibiting virus entry. In clinical trials, the seroconversion rate of neutralizing antibodies reached 100% after vaccination, and antibody levels were maintained over an extended period, providing reliable immune protection against severe cases of hand, foot, and mouth disease. Upon subsequent exposure to live EV71, the immune system can rapidly recognize and eliminate the virus, thereby preventing EV71-associated hand, foot, and mouth disease (HFMD) and its severe neurological complications.

The T-cell immune response is evidenced by a marked increase in IFN- γ -secreting cells following stimulation of peripheral blood mononuclear cells with EV71 VP1 peptides (e.g., SSIGDSVSRAL). Gene expression analysis revealed upregulation of genes associated with T-cell activation, differentiation, and memory formation (such as JAKMIP1 and GZMK), suggesting the induction of effector T-cell memory.

12.3 Clinical Efficacy/Immunogenicity

A randomized, double-blinded, placebo-controlled and multi-center Phase III (*Phase III clinical trial for Enterovirus Type 71 Vaccine, Inactivated*) clinical trial was performed to evaluate the efficacy, safety and immunogenicity of the vaccine among 12,000 healthy infants and children aged from 6 to 71 months, who were administrated with the vaccine following Day 0, 28 schedule.

(1) Efficacy

The efficacy of this product was evaluated based on the incidence rate of HFMD caused by EV71 in all participants after administering either the vaccine or the placebo during one-year active surveillance.

As a result, the vaccine efficacy against EV71-associated HFMD was 97.3% (95%CI: 92.7, 99.0) using full analysis set (FAS) analysis (N= 12,000), and the vaccine efficacy was 97.3% (95%CI: 92.6, 99.0) using per protocol set (PPS) analysis (N=10,980) one year after primary immunization. The vaccine efficacy among the all age groups and different age subgroups were showed in Table 1 - 2. This study did not observed the protection of this vaccine to the HFMD

caused by other enterovirus (i.e. Coxsackievirus A16) infection.

Table 1 Vaccine efficacy against HFMD after full-course immunization in one year (FAS analysis)

Items	EntroVac® (N=6000)			Placebo (N=6000)			Efficacy(95%CI)
	Cases	%	95%CI	Cases	%	95%CI	
HFMD caused by EV71	4	0.07	0.02-0.17	148	2.47	2.09-2.89	97.3 (92.7, 99.0)
Severe HFMD caused by EV71	0	0.00	0.00-0.07	2	0.04	0.00-0.13	100.0(.,.)
HFMD caused by CA16	45	0.75	0.55-1.00	52	0.87	0.65-1.13	13.5 (-28.7, 41.8)
HFMD caused by other viruses	105	1.75	1.43-2.11	128	2.13	1.78-2.53	18.0 (-5.9, 36.5)

Table 2 Efficacy of HFMD Caused by EV71 for all recipients at different ages after full-course Immunization

Ages	Vaccine Group (N=919-1611)			Placebo Group (N=906-1623)			Efficacy
	Cases	Incidence %	95%CI	Cases	Incidence %	95%CI	95%CI
6-11 months	0	0	0.00-0.23	38	2.4	1.69-3.26	100.0(.,.)
12-23 months	2	0.1	0.02-0.45	51	3.1	2.35-4.11	96.0(83.8,99.0)
24-35	2	0.2	0.02-	40	2.9	2.08-	95.1(79.8,98.8)

months			0.53			3.94	
36-71 months	0	0	0.00-0.40	16	1.8	1.01-2.85	100.0(.,.)

The efficacy is conservatively estimated to be 93.77% (95%CI: 88.34, 96.67) two years after full-course immunization.

(2) Immunogenicity and Immune Persistence

The immunogenicity and immune persistence till two years after immunization were assessed in an immunogenicity subgroup (N=1,100) of the phase III clinical trial. The seroconversion rates and the geometric mean titers (GMT) of neutralizing antibodies (anti-genotype C4) among the immunized subjects remained at a high level during the two-year study period, which displayed good protective efficacy against EV71 infection and immune memory of this product. The results were listed on Table 3.

Table 3 The GMT and seroconversion rate of NAb at different time after whole-course immunization in immunogenicity subgroup (PPS)*

	Item	**GMT before immunization**	**GMT after 2 doses immunization**				
			1 month	**6 months**	**12 months**	**18 months**	**24 months**
		N=549	N=483	N=453	N=311	N=248	N=242
EV71 vaccine	**GMT(95%CI)**	5.87 (5.30-6.51)	224.37 (197.95-254.32)	118.0 (102.85-135.38)	99.71 (85.22-116.65)	572.16 (468.72-698.42)	728.48 (590.87-898.14）
	Number of	57 (10.38)	483 (100.0)	450 (99.34)	306 (98.39)	248 (100.00)	240 (99.17)

	Positive (%)						
Placebo		N=550	N=496	N=456	N=301	N=271	N=277
	GMT(95%CI)	6.34 (5.67-7.10)	7.44 (6.47-8.56)	20.19 (16.42-24.82)	16.36 (13.01-20.58)	37.74 (27.37-52.05)	74.00 (52.88-103.58)
	Number of Positive (%)	65 (11.82)	73 (14.72)	173 (37.94)	114 (37.87)	156 (57.56)	180 (64.98)

*The neutralization antibody was detected based on the micro-neutralization assay on Vero cell (cytopathogenic effect inhibition assay, CPEI) according to World Health Organization standard method.

Additionally, the cross-neutralization test against 9 strains of EV71 virus was also performed using the serum samples collected from the participants (N=160) at 0, 56 and 360 days post-immunization. The strains include Genotype A (BrCr strain), Genotype C (subtype C1, C2, C3, C4, C5) and Genotype B (subtype B3, B4, B5). The results show that this EV71 vaccine derived from C4 genotype strain could be effectively used to induce adequate protective immunity against infection by most of the predominant circulating EV71 strains.

13. PHARMACOKINETICS

Pharmacokinetics studies were not performed as these are not considered applicable to vaccines and is in accordance to the EMA "Note for guidance on preclinical pharmacological and toxicological testing of vaccines" and WHO guidelines on nonclinical evaluation of vaccines.

14. PRECLINICAL STUDIES

Preclinical safety data reveal no special hazard based on conventional studies of single-dose toxicity (acute toxicity) test, systemic active allergy (sensitization) test, repeat-dose toxicity test and antinuclear antibody test.

15. STORAGE

Store and ship at 2-8℃, protected from light. Do not freeze.

Keep medicines out of reach of children.

16. PACKAGING

Vial:

- 0.5 mL suspension in vial
- Pack of 1 vial

Prefilled syringe

- 0.5 mL suspension in prefilled syringe
- Pack of 1 prefilled syringe

17. SHELF LIFE

36 months.

18. PRODUCT REGISTRATION HOLDER

Toppharma Marketing (M) Sdn Bhd

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46100 Petaling Jaya, Selangor, Malaysia

19. MANUFACTURER

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