Enterovirus Type 71 Vaccine (Vero Cell), Inactivated

[Brand Name / Product Name]

EVnyx Enterovirus Type 71 Vaccine (Vero Cell) Inactivated Suspension for Injection 480U/0.5mL in Prefilled Syringe

[Composition]

1 dose (0.5 mL) contains:

Enterovirus 71, H07 strain (inactivated)__480 U

Aluminium (as aluminium hydroxide)__0.65 mg

Other Ingredients: Sodium chloride, Disodium hydrogen phosphate, Sodium dihydrogen phosphate and Water for injection.

No preservative is used in EVnyx.

[Description]

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

[Indication]

EVnyx is indicated for active immunization of children aged from 6 months to 71 months against EV71, and is used to prevent hand, foot and mouth disease caused by EV71 infection.

EVnyx should be used in accordance with official recommendations.

[Recommended Dosage]

Individuals aged 6 months to 71 months of age.

Two doses of 0.5 mL each should be administered for primary immunization.

The use of this vaccine shall be at least 1 month apart.

[Route of Administration]

EVnyx should be administered by intramuscular injection in the deltoid region of the upper arm.

[Instruction for Use]

Shake thoroughly before use. Do not use if it shows abnormalities, such as crack, illegible label, exceeding expiry date or foreign matters in the container.
Use immediately after open.

[Adverse Reactions]

1. Clinical Trial

A total of 13,083 children were enrolled in several clinical trials in China, and 7,233 were vaccinated with different dose of EVnyx. In the pivotal study, 10,077 children aged 6 to 35 months were enrolled, and 898 children aged 36 to 71 months for immunogenicity bridging were enrolled.

According to the grading standard of adverse reaction incidence from Council for International Organizations of Medical Sciences (CIOMS), i.e., very common (≥10%), common (1% - 10%, 1% was inclusive), uncommon (0.1% - 1%, 0.1% was inclusive), rare (≥ 0.01% and < 0.1%) and very rare (< 0.01%), all adverse reactions were summarized and described as follows.

Systemic adverse reactions:

Very common: Pyrexia, diarrhea

Common: Anorexia, irritability, nausea / vomiting, fatigue, hypersensitivity

Uncommon: Rash, cough, runny nose, cold / upper respiratory tract infection symptoms

Local adverse reactions:

Common: Erythema, swelling, induration, pain, itching

Uncommon: Rash

Serious adverse reactions:

One case of severe adverse reaction occurred during the clinical trial of the vaccine, which was anaphylactoid purpura.

Phase III clinical trial was carried out in 10,077 healthy children (6 to 35 months of age) who received two doses of EVnyx or placebo on day 0 and day 28. Among them, 5,044 subjects were vaccinated with EVnyx and the safety monitoring lasted for one year. The incidence rate of adverse reactions of EVnyx group and the placebo group were 51.70% and 52.77%, respectively within 56 days after vaccination. The rates of solicited systemic adverse reactions were 45.56% and 46.53%, respectively, including pyrexia, diarrhea, and loss of appetite, nausea /vomiting, irritability, mainly transient. The incidences of solicited local adverse reactions were 13.88% and 13.59%, respectively, and the most common were redness, induration, pain, swelling and pruritus at the injection site. Most of the adverse reactions were Grade 1 (mild), lasting for less than 3 days and self-remission. The rates of unsolicited adverse reactions were less than 1% for both groups. There were no significantly differences between the vaccine group and the placebo group for Grade 3 and above adverse reactions. The rates of adverse reactions were higher after the first dose, and no increase was observed when given the second dose.

In the domestic extended population trial, 599 healthy children aged 36-71 months were vaccinated with two doses of EVnyx or positive control vaccine according to day 0, 30 immunization schedule. Among them, 300 subjects were vaccinated with EVnyx and the safety monitoring lasted for six months. The incidence rate of adverse reactions of EVnyx and the positive control vaccine were 47.00% and 44.82%, respectively. All adverse reactions occurred in this trial are solicited. The incidences of systemic adverse reactions were 40.67% and 42.14%, respectively, including pyrexia, loss of appetite, fatigue, irritability, diarrhea, nausea /vomiting, allergic reaction, etc., and mainly grade 1 or 2 pyrexia (mild and moderate). The incidence rate of solicited local reactions is 11.67% and 7.69% respectively, the most common were pain, redness, induration, swelling and pruritus in the injection site. Most of the adverse reactions were Grade 1 (mild) pain.

2. Post-marketing Experience

Except for the adverse reactions reported in the above-mentioned clinical trials, the following adverse reactions have been identified during post-marketing use of EVnyx. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

General disorders and administration site conditions: pyrexia (> 39.1°C), pruritus, chill

Skin and subcutaneous tissue disorders: macule, papule, rash maculo-papular, rash vesicular, urticaria, dermatitis allergic

Gastrointestinal disorders: enteritis

Nervous system disorders: febrile convulsion

3. Others

The following adverse reactions have been observed during the application of other inactivated viral vaccines: (1) lymphadenopathy at the injection site; (2) allergic / allergic reactions caused by any component of the vaccine: anaphylactic shock; (3) thrombocytopenic purpura, etc. Although the above mentioned adverse reactions were not found during clinical trials of this vaccine, attention on the adverse reactions mentioned above should be paid while using EVnyx.

If any recipient has unexpected adverse reactions that are not mentioned above, please contact the doctor immediately.

[Symptoms and Treatment of Overdose]

No case of overdose has been reported. In the event of an overdose, the individual should be monitored and provided with symptomatic treatment as appropriate.

[Contraindications]

Do not use under the following conditions:

(1) Allergic to any component of the vaccine.

(2) Pyrexia, acute diseases and acute onset of any chronic diseases.

(3) Seriously chronic diseases, allergic constitution.

[Warning and Precautions]

(1) This vaccine should under no circumstances be administered intravascularly.

(2) Epinephrine and other drugs and equipment shall be prepared for first aid in case of occasional severe allergic reaction. Individuals should be observed for at least 30 minutes on site after vaccination.

(3) Be cautious when using EVnyx in the following circumstances：

1) Bleeding is possible after intramuscular injection among recipients suffered from thrombocytopenia or hemorrhagic disease.
2) The immune response of vaccination may be attenuated if patients are receiving immunosuppressive therapy or with immunodeficiency. Avoid using EVnyx during immunosuppressive therapy. EVnyx is recommended even under the attenuated immune response condition for patients with chronic immunodeficiency.
3) Patients suffering from uncontrolled epilepsy or progressive neurological disorders, such as Guillain-Barre Syndrome.

(4) Like other vaccines, the protective effect of EVnyx may not reach 100% for all recipients.

(5) Avoid expose vaccine to the disinfectant during use.

[Use in Pediatric Patients with Renal or Hepatic Impairment]

Vaccination should be considered on an individual basis based on the physician's assessment of the benefits and risks based on the condition of disease since no clinical data has been obtained in pediatric patients with renal or hepatic impairment.

[Effects on Ability to Drive and Use Machine]

EVnyx generally has no or negligible influence on the ability to drive and use machines. However, some of the adverse may temporarily affect the ability to drive or use machines.

[Incompatibilities]

In the absence of compatibility studies, this vaccine must not be mixed with other medicinal products.

[Interactions with Other Medicaments]

(1) Administration with other vaccines at the same time: The co-administration of EVnyx with measles-mumps-rubella vaccine and live-attenuated Japanese encephalitis vaccine had no interference with immunogenicity and safety, compared with separate administration of these vaccines. Same results were obtained for the simultaneous administration of EVnyx with hepatitis B vaccine and group A meningococcal polysaccharide vaccine.

(2) Immunosuppressive medicines: Immune response may be reduced by immunosuppressants, chemotherapy drugs, antimetabolites, alkylating agents, cytotoxic drugs, corticosteroids, etc.

(3) Patients receiving treatment: for people who are using drugs, in order to avoid possible drug interactions, consult the doctor before administration of EVnyx.

[Pregnancy and Lactation]

Pregnant and lactating women

No data are available on the use of EVnyx in pregnant or lactating women to inform a vaccine-associated risk. This vaccine has not been studied in pregnant or lactating women. As the indicated population for EVnyx is children aged 6 months to 71 months old and it is not intended for use in pregnant women.

[Pharmacodynamics]

Mechanism of Action

After inoculation, this vaccine can induce immunity against enterovirus 71 (EV71), including high levels of neutralizing antibodies and EV71-specific T-cell immune responses, thereby preventing hand, foot, and mouth disease (HFMD) caused by EV71 infection. The neutralizing antibodies induced by the vaccine can block the binding of the virus to host receptors, thereby inhibiting viral entry.

In clinical trials, among subjects who were seronegative for EV71 neutralizing antibodies at baseline (neutralizing antibody titer <1:8), the seroconversion rate of neutralizing antibodies reached 98.58% after vaccination. Antibody levels were maintained for up to 5 years following vaccination, providing sustained immune protection against HFMD caused by EV71 infection.

Following the two-dose vaccination regimen, peripheral blood mononuclear cells showed significantly increased numbers of interferon-γ (IFN-γ)- and interleukin-4 (IL-4)-secreting cells following stimulation with EV71. These findings indicate that the vaccine can induce a balanced Th1/Th2 T-cell immune response.

The mechanism of action of this vaccine involves the simultaneous induction of EV71-specific humoral immunity and cell-mediated immunity.

Efficacy

In a Phase III clinical trial done to evaluate safety, immunogenicity and immune persistence, 2 doses EVnyx was administered with 28 days interval. The primary endpoint of clinical trial was the occurrence of clinical-confirmed HFMD associated with EV71 within the case monitoring period (within one year) of the subjects administrated with EVnyx or placebo. In the Full Analysis Set (FAS, N=10,069), the vaccine efficacy in preventing HFMD of any severity caused by EV71 infection within 1 year after completion of the full vaccination series was 94.6% (95% CI: 86.6%–97.8%). In the Per-Protocol Set (PPS, N=9,165), the vaccine efficacy was 94.3% (95% CI: 86.1%–97.7%). The protective efficacy for the overall population and by age subgroup are presented in Tables 1–2 below.

Table 1 Efficacy of the vaccine against EV71-associated HFMD within 1 year after immunization (FAS)

Analysis Item	Vaccine Group （4973.2 person-year）	Placebo Group （4873.0 person-year）	Efficacy (%) （95%CI）

	No. of case(s)	Incidence density (%)	95%CI	No. of cases	Incidence density (%)	95%CI	
HFMD caused by EV71 infection	5	0.101	0.042-0.242	90	1.847	1.502-2.271	94.6(86.6-97.8)
Severe HFMD caused by EV71 infection	0	0.000	0.000-0.161	8	0.164	0.082-0.328	100.0(42.6-100.0)
HFMD caused by CA16 infection	264	5.308	4.705-5.989	284	5.828	5.188-6.547	8.9(-7.7-23.0)
HFMD caused by other Enterovirus infection	244	4.906	4.328-5.562	281	5.766	5.130-6.482	14.9(-1.0-28.3)

Table 2 Efficacy of the vaccine against EV71-associated HFMD within 1 year after immunization by age groups (FAS)

Age Group	Vaccine Group（4973.2 person-year）				Placebo Group（4873.0 person-year）				Efficacy	95% CI
	No. of case(s)	No. of person-year	Incidence density (%)	95%CI	No. of cases	No. of person-year	Incidence density (%)	95%CI		
6-11m	3	1,177.4	0.255	0.082-0.790	17	1,155.9	1.471	0.914-2.366	82.7	40.9-94.9
12-23m	2	2,452.9	0.082	0.020-0.326	57	2,397.4	2.378	1.834-3.082	96.6	86.0-99.2
24-35m	0	1,342.9	0.000	-	16	1,319.7	1.212	0.743-1.979	100.0	-

Immune Persistency

In another Phase III clinical trial, immune persistency was observed for two years among subjects in immunogenicity subgroup to evaluate the seroconversion rate and geometric mean titer (GMT) after two doses of vaccine. Outcome for immune persistence analysis demonstrated that, 26 months after the first vaccination, the seropositive rate (≥ 1:8) was 87.37% (99.65% at 56 days, 99.65% at 8 months, and 99.65% at 14 months after the first vaccination) and the seroconversion rate (≥ 1:8) was 69.47% (95.09% at 56 days, 89.47% at 8 months, and 86.32% at 14 months after the first vaccination). Meanwhile, the GMT was 1:40.9 (1:229.37 at 56 days, 1:106.42 at 8 months, and 1:94.38 at 14 months after the first vaccination), and the GMI was 4.06 (22.90 at 56 days, 10.63 at 8 months, and 9.42 at 14 months after the first vaccination) in the vaccine group. Statistically significant differences were observed in the seropositive rates (≥ 1:8), seroconversion rates (≥ 1:8), GMTs, and GMIs at 56 days, 8 months, 14 months, and 26 months in the vaccine group; the seropositive rate (≥ 1:8),

seroconversion rate (≥ 1:8), GMT, and GMI were all greater at 56 days, 8 months, and 14 months than at 26 months. This indicated that a relatively higher level EV71 neutralizing antibody level was still maintained in year 2 post-immunization.

Following the previous Phase III clinical trial, further follow-up has been conducted to assess the five-year immune persistency of EVnyx. Result showed that, with the antibody titer of 1:8 as the positive critical value, the seropositive rate of neutralizing antibodies at 64 months after immunization was 94.34% in the vaccine group and 71.43% in the placebo group. Meanwhile, the GMT of neutralizing antibodies at 64 months after immunization was 141.42 in the vaccine group and 71.83 in the placebo group. Both the seropositive rate and the GMT of neutralizing antibodies at each time point after immunization were statistically greater in the vaccine group than in the placebo group, and the differences were statistically significant. The study showed favourable finding that EVnyx has relatively good immunity persistence, and there is no evidence of the need for booster immunization.

Table 3 Antibody level and seroconversion rate at different time points after full immunization (PPS)*

Analysis item		**Pre-vaccination**	**Post-vaccination (2 doses)**			
			1 month	**7 months**	**13 months**	**25 months**
Vaccine Group		N=579	N=579	N=550	N=528	N=480
	GMT (95%CI)	7.49 (6.58-8.52)	165.79 (145.85-188.45)	88.77 (77.76-101.33)	92.12 (81.40-104.25)	56.34 (48.79-65.06)
	Seroconversion (%)	-	553(95.51)	506(92.00)	476(90.15)	365(76.04)
	Positive number (%)	87 (15.03)	572 (98.79)	546 (99.27)	524 (99.24)	429 (89.38)
Placebo Group		N=571	N=571	N=548	N=522	N=481
	GMT (95%CI)	8.23 (7.19-9.43)	8.90 (7.69-10.29)	12.50 (10.58-14.77)	13.19 (11.15-15.60)	14.65 (12.51-17.15)
	Seroconversion (%)	-	20(3.50)	77(14.05)	107(20.50)	119(24.74)
	Positive number (%)	103 (18.04)	112 (19.61)	154 (28.10)	181 (34.67)	195 (40.54)

* Neutralizing antibody was determined by Vero cell culture micro neutralization test (cytopathic method) according to the standard method of WHO. Seropositive is defined as a neutralizing antibody titer ≥1:8. Seroconversion is defined as a change from <1:8 to ≥1:8, or a ≥4-fold increase in titer from a baseline of ≥1:8.

Table 4. Antibody level and seroconversion rate (1:8) (PPS) 1 month after full immunization schedule

Population	Analysis item	36-71 months EVnyx (T)	36-71 months Control Vaccine (C1)	6-35 months EVnyx (C2)	Difference/Ratio (T-C1) (95%CI)	Difference/Ratio (T-C2) (95%CI)

Susceptible	**N**	182	166	234		
	Seroconversion (%)	182 (100.00)	166 (100.00)	234 (100.00)	0.00	0.00
		(97.99, 100.00)	(97.80, 100.00)	(98.44, 100.00)	(-2.07, 2.07)	(-2.07, 1.62)
	GMT (95%CI)	370.0 (312.6, 438.0)	296.2 (248.2, 353.4)	176.5 (152.1, 204.9)	1.25 (0.98, 1.60)	2.10 (1.67, 2.62)
All population	**N**	288	293	274		
	Seroconversion (%) (95%CI)	275 (95.49) (92.40-97.57)	252 (86.01) (81.50-89.77)	270 (98.54) (96.30, 99.60)	9.48 (4.92, 14.37)	-3.05 (-6.29, -0.25)
	GMT (95%CI)	1012.3 (832.1, 1,231.5)	870.8 (717.0, 1,057.6)	294.5 (240.9, 360.1)	1.16 (0.88, 1.53)	3.44 (2.60, 4.55)

Note: T: EVnyx group of 36-71 months, C1: Positive control group of 36-71 months, C2: EVnyx control group of 6-35 months. Non-inferiority Margin: Lower limit of 95% CI of difference of seroconversion rate (test group – control group) is greater than -5%; Lower limit of 95% CI of GMT ratio (test group /control group) is greater than 0.67. Seroconversion is defined as a change from <1:8 to ≥1:8, or a ≥4-fold increase in titer from a baseline of ≥1:8.

For safety data of the above clinical trial, please see [**Adverse Reactions].**

Interchangeability with Another Manufacturer's EV71 Vaccine

A randomized, controlled, open-label clinical trial (Study No. EV71-SD-2018-01) was conducted in 300 healthy infants and young children aged 6 to 35 months to evaluate the immunogenicity and safety of interchangeable vaccination with two licensed inactivated EV71 vaccines: EVnyx (Vero cell, Sinovac) and an inactivated EV71 vaccine produced by the Institute of Medical Biology, Chinese Academy of Medical Sciences (IMBCAMS; human diploid cell). Subjects were randomized 1:1:1:1 to four groups receiving two doses on Days 0 and 30 according to the following schedules: EVnyx / EVnyx Group, n=75; IMBCAMS / IMBCAMS Group, n=75; EVnyx / IMBCAMS Group, n=74; and IMBCAMS / EVnyx Group, n=74. Serum EV71 neutralizing antibody was measured 30 days after the second dose.

Based on the per-protocol set (PPS), seroconversion rates 30 days after the second dose were all above 98% across the four groups, with no statistically significant differences. Detailed immunogenicity results are shown in Table 5.

Table 5. Immunogenicity 30 days after the second dose in the interchangeability study (PPS)

Parameter	EVnyx / EVnyx group (N=68)	IMBCAMS / IMBCAMS group (N=67)	EVnyx / IMBCAMS group (N=68)	IMBCAMS / EVnyx group (N=64)	*P* value
Seroconversion rate (95%CI)	100.00 (94.72-100.00)	100.00 (94.64-100.00)	98.53 (92.08-99.96)	98.44 (91.60-99.96)	0.6132
GMT (95%CI)	255.71 (187.66, 348.43)	220.62 (167.34, 290.86)	211.42 (155.14, 288.11)	460.49 (355.95, 595.73)	<0.0001

GMT: Geometric Mean Titer. Seroconversion is defined as a change from <1:8 to ≥1:8, or a ≥4-fold increase in titer from a baseline of ≥1:8. EVnyx: inactivated EV71 vaccine (Vero cell, Sinovac); IMBCAMS: inactivated EV71 vaccine (human diploid cell, Institute of Medical Biology, Chinese Academy of Medical Sciences).

The overall incidence of adverse reactions was comparable across the four groups (25.33% in EVnyx / EVnyx Group, 33.78% in IMBCAMS / IMBCAMS Group, 24.32% in EVnyx / IMBCAMS Group and 24.32% in IMBCAMS / EVnyx Group respectively; p=0.5243), with Grade 1 and Grade 2 reactions predominating. Pyrexia was the most frequently reported systemic reaction (overall incidence 21.55%), and the overall incidence of local reactions was low (2.02%). Seven serious adverse events were reported across the four groups, none of which were assessed as related to vaccination, with no statistically significant differences between groups (p=0.6834).

Based on above results, EVnyx could be interchangeable with the licensed inactivated enterovirus type 71 vaccine (human diploid cell) manufactured by the Institute of Medical Biology, Chinese Academy of Medical Sciences. No data are available on the interchangeability of EVnyx with other brands of EV71 vaccines.

[Pharmacokinetics]

Not applicable.

[Preclinical Safety Data]

Preclinical data reveal no special hazard for humans.

[Storage]

Store between 2°C to 8°C. Protect from light.

Do not freeze.

[Dosage Form and Packaging Available]

0.5 mL suspension in a pre-filled syringe. Pack of 1 pre-filled syringe.

[Shelf Life]

36 months.

Do not use if it exceeds expiry date.

[Product Registration Holder]

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