Inlive®

Enterovirus Type 71 Vaccine (Vero Cell), Inactivated

Suspension for Intramuscular Injection

[Name of the Medicinal Product]

Generic Name: Enterovirus Type 71 Vaccine (Vero cell), Inactivated

Trade Name: Inlive®

English Name: Enterovirus Type 71 Vaccine (Vero Cell), Inactivated

[Composition and Description]

Per 0.5 mL dose contain Inactivated enterovirus type 71 480 u.

Inlive®, inactivated Enterovirus type 71 vaccine is derived from Enterovirus type 71 virus (EV71 H07 Strain) cultured in African green monkey kidney cells (vero cells), followed by culture, harvest, inactivation, concentration, purification and aluminum hydroxide adsorption. It is a milky-white suspension. Stratified precipitate may form which can be dispersed by shaking.

No clumps shall be found on shaking.

Active Ingredient: Inactivated EV71 virus antigen

Excipients: Aluminum hydroxide, sodium chloride, disodium hydrogen phosphate, sodium dihydrogen phosphate, water for injection.

Free of Preservative.

[Target Groups for Vaccination]

Susceptible people aged from 6 months to 71 months of age.

[Therapeutic Indication]

Inlive® can induce body to generate immunoreaction against EV71 virus, and can be used to prevent Hand-Foot-Mouth Disease (HFMD) caused by EV71 virus. Inlive® cannot be used to prevent HFMD caused by other enteroviruses (such as CoxA 16, etc.).

[**Contraindications**]

(1) Allergic to any component of the vaccine, including gentamycin sulfate.

(2) Fever, acute diseases and acute paroxysm of any chronic diseases.

(3) Seriously chronic diseases, allergic constitution.

[Presentation]

Each syringe contains 0.5 mL. Single dose of 0.5 mL contains EV71 neutralizing antibody titer no less than 3.0 EU (EU: NAT Unit) or antigen content no less than 480U/0.5mL.

[Administration and Dosage]

ADMINISTRATION: Ready to use suspension for intramuscular injection. The preferred site is the deltoid muscle of the upper arm.
Schedule and dosage: two doses of 0.5 mL each, at 1-month interval.
Booster immunization is not confirmed.

[Adverse Reactions]

1. Clinical Trial

A total of 15,357 children were enrolled in several clinical trials in China, and 8,743 were vaccinated with different dose of Inlive®. 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 criteria 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: Fever, diarrhea
Common: Loss of appetite, dysphoria, nausea/vomiting, fatigue, hypersensitivity
Uncommon: Rash, cough, rhinorrhea, influenza/upper respiratory tract infection symptoms
Local adverse reactions:
Common: Redness, induration, pain, pruritus
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 10,007 healthy infants (6 to 35 months of age) and the subjects were divided randomly into the vaccine (400U) or placebo group were inoculated two doses with a 28-days interval apart. The safety monitoring lasted for one year. The frequency of adverse reaction (AE) of Inlive® group and placebo group were 51.70% and 52.77%, respectively within 56 days after vaccination. The solicited systemic adverse reactions rates were 45.56% and 46.53%, respectively, such as fever, diarrhea, and loss of appetite, nausea, irritability, mainly temporal fever and diarrhea. The solicited local adverse reactions were 13.88% and 13.59%, respectively, such as redness, induration, pain, swelling and itching. Most of the cases were mainly rated as Grade 1, lasting for less than 3 days and self-remission. The rates of non-solicited reactions were less than 1% for both groups. All AEs, which were rated as Grade III,

had no significantly statistic differences between vaccine group and placebo group. The rates of AEs were higher after inoculation of the first dose, and no increase was observed when the following dose is given.

In the domestic extended population trial, 599 healthy children aged 36-71 months were vaccinated with two doses of Inlive® or positive control vaccine according to day 0, 30 immunization schedule. Among them, 300 subjects were vaccinated with Inlive® and the safety monitoring lasted for six months. The incidence rate of adverse reactions of Inlive® 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 fever, loss of appetite, irritability, diarrhea, nausea /vomiting., and mainly grade 1 or 2 fever (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 events have been identified during post-marketing use of Inlive®. Because these adverse events 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: fever (>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 AEs have been observed during the application of other inactivated viral vaccines:

(1) Lymph node enlargement on the injection site; (2) urticaria, allergic rash or purpura, allergic shock caused by any component of vaccine (3) seizures (with or without fever). Although the mentioned AEs above were not found during clinical trials of the vaccine, cautions should be taken while using Inlive®.If any recipient has unexpected adverse reactions that are not mentioned above, please contact the doctor immediately.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reaction via farmakovigilans@kalventis.com

and 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
Email: pv-center@pom.go.id
Phone: +62-21-4244691 Ext.1079
Website: https://e-meso.pom.go.id/.

[Precautions]

(1) Must not be intravenous injection.
(2) Adrenalin and other first aid medicine should be prepared at the vaccination place, in case of seriously allergy reactions. The vaccinated recipient should not leave until 30 minutes after vaccination.
(3) Be cautious when using Inlive® in the following circumstances：
    1) Bleeding is possible after intramuscular injection if the recipients suffer from thrombocytopenia or hemorrhagic disease.
    2) The immune response of vaccination may be attenuated, if patients are receiving immunosuppressive therapy or the patients are immune deficiency. Patients who are receiving immunosuppressive therapy should get vaccination after therapy. Although immune response may be limited for patients with chronic immune deficiency, the vaccination of Inlive® is still recommended.
    3) The patients who are suffering from epilepsia or nervous system diseases, such as Guillain-Barre Syndrome.
(4) Like other vaccines, the protective efficacy of Inlive® may not reach 100% for all recipients.
(5) Put the vaccine out of children’s reach.
(6) Shake scattered before use. Do not use the product if any crack of the container, label is blurred, or foreign matters in the container.
(7) Do not let disinfectant contact vaccine during injection or when the product is opened.
(8) Do not freeze. Use immediately after open.
(9) To make sure the immunization effectiveness, the person who receives human immunoglobulin and gets vaccination should conduct these two activities at least 1 month apart.

[Drug Interactions]

(1) Co-administration with other vaccines: Inlive® can be administered simultaneously with measles-mumps-rubella vaccine, live-attenuated Japanese encephalitis vaccine, hepatitis B vaccine and group A meningococcal polysaccharide vaccine.
(2) Drug of immunosuppression: Immune response may be reduced by immunosuppressant, chemical therapy drug, anti-metabolic drug, alkylating agent,

cytotoxin, corticosteroids, etc.

(3) Patients under treatment: Consult the doctor before inoculation.

(4) Observational study conducted by Shanghai CDC indicated that Inlive® administration simultaneously with other vaccines (Oral rotavirus vaccine (ORV), Inactivated poliovirus vaccine (IPV), Groups A and C meningococcal polysaccharide conjugate vaccine (MPV-AC), AC+Hib (Haemophilus influenzae type b) (AC-Hib), Influenza) did not increase the frequency or severity of adverse events.

[Overdose]

No cases of overdose were reported.

[Non-clinical Safety Data]

Toxicity in animal studies (acute toxicity, repeated-dose toxicity) do not indicate any toxic effects or target organ toxicity.

[Clinical Trials]

(1) Phase III clinical trial for registration

A phase III randomized, double-blind, placebo-controlled, multicenter clinical trial was conducted to evaluate the safety, efficacy and immunogenicity, in which 10,007 healthy infants and young children (6 to 35 months of age) were inoculated two doses with a 28-day interval apart.

(1) Efficacy

The primary endpoint of this clinical trial was the incidence rate of EV71-associated hand, foot, and mouth disease or herpangina (within one year).

Cases Definition: Clinical diagnosis of HFMD and confirmed positive by pathogen detection (Enterovirus RNA on fluorescence quantitative PCR assay).

All cases had been confirmed by panel as well as repeated testing on pathogen detection.

Results: for FAS dataset (10069 subjects), the protective efficacy against EV71-associated HFMD was 94.6% (95%CI: 86.6-97.8); for PPS dataset (9165 subjects), efficacy was 94.3% (95%CI: 86.1-97.7). The protective efficacy, incidence density and effect index of EV71 vaccine for all participants and by age groups were shown in Table 1 to Table 4. The incidence density and protective efficacy were calculated by Poisson regression model.

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

Analysis	Vaccine Group (4973.2 person-year)	Control Group (4873.0 person-year)	Protection Rate (%)

	No. of Cases	Incidence density (%)	95%CI	No. of Cases	Incidence density (%)	95%CI	(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 Incidence density of vaccine against EV71-associated HFMD within 1 year after immunization

	FAS		PPS	
	Vaccine Group	Placebo Group	Vaccine Group	Placebo Group
Incidence density (%)	5(0.101)	90(1.847)	5(0.110)	87(1.936)
95% CI	0.042-0.242	1.502-2.271	0.046-0.263	1.569-2.388
No. of person-years observed	4973.2	4873.0	4568.9	4494.9

Table 3 Effect index of vaccine against EV71-associated HFMD within 1 year after immunization

		FAS		PPS	
		Statistics	P	Statistics	P
Effect index	RR(95%CI)	18.35(7.46-45.13)	<0.0001	17.67(7.18-43.52)	<0.0001

Table 4 Protective efficacy of vaccine against EV71-associated HFMD within 1 year after immunization by age groups (FAS)

Age Group	Vaccine Group（4973.2 person-year）				Control Group（4873.0 person-year）				Protective efficacy	Protective efficacy (%)
	No. of Case	No. of person-year	Incidence density (%)	95%CI	No. of Case	No. of person-year	Incidence density (%)	95%CI	%	(95%CI)

6-11m	3	1177.4	0.255	0.082-0.790	17	1155.9	1.471	0.914-2.366	82.7	40.9-94.9
12-23m	2	2452.9	0.082	0.020-0.326	57	2397.4	2.378	1.834-3.082	96.6	86.0-99.2
24-35m	0	1342.9	0.000	-	16	1319.7	1.212	0.743-1.979	100.0	-

A one-year extended follow-up study had been conducted (Vaccine Group 4881.0 person-year, in compare with Control Group 4771.8 person-year), and the protective efficacy of vaccine against EV71-associated HFMD within the second year after immunization was 95.1% (95%CI: 63.6-99.3).

(2) Immunogenicity and persistence study

In order to evaluate the immune persistence of Inlive®, a two-year study had been conducted on data from immunogenicity cohort, which evaluated the geometric mean titer (GMT) of the EV71 neutralizing antibody and the seroconversion rate (defined as post dose GMT ≥1:8 for negative recipients, or 4 fold increase of GMT after vaccination for positive recipients).

The statistics were shown in **Table 5**.

Table 5 Antibody level and seroconversion rate at different time points after immunization (PPS)*

		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)
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)

* Cytopathic inhibition assay was used to test neutralize antibody which was recommended by WHO

(2) Clinical trial for extended population

The clinical trial for extended population was conducted in China in a randomized, double-blind, positive control, bridging design to evaluate the immunogenicity and safety of Inlive® in children aged 36-71 months.

A total of 600 children aged 36 to 71 months were randomized to receive two doses of Inlive® or two doses of positive control with a ratio of 1:1, and 300 infants aged 6-35 months were administrated two doses of Inlive® in a 0, 30 days immunization schedule. After one month of two doses Inlive® administration for children aged 36-71 months, the seroconversion rates of anti-EV71 neutralization antibody with 1:8, 1:16, 1:32 and 1:64 were 100.00%, 98.90%, 97.25% and 93.96%, respectively, and the GMT is 370.0 among susceptible children (pre-immunization neutralization antibody< 1:8) in PPS. Seroconversion rate and GMT in Inlive® group aged 36-71 months were non-inferior to the positive control group aged 36-71 months and group aged 6-35 months.

The seroconversion rates of anti-EV71 neutralization antibody with 1:8, 1:16, 1:32 and

1:64 were 95.49%, 94.79%, 93.75% and 91.67%, respectively, and the GMT is 1,012.3 among all population. Results of seroconversion rate and GMT were shown in Table 6.

Table 6. Antibody level and seroconversion rate (1:8) (PPS) 1 month after full immunization schedule

Population	Analysis item	36-71 months Inlive® (T)	36-71 months Control Vaccine (C1)	6-35 months Inlive® (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	370.0	296.2	176.5	1.25	2.10
	(95%CI)	(312.6, 438.0)	(248.2, 353.4)	(152.1, 204.9)	(0.98, 1.60)	(1.67, 2.62)
All population	**N**	288	293	274		
	Seroconversion (%)	275 (95.49)	252 (86.01)	270 (98.54)	9.48	-3.05
	(95%CI)	(92.40-97.57)	(81.50-89.77)	(96.30, 99.60)	(4.92, 14.37)	(-6.29, -0.25)
	GMT	1012.3	870.8	294.5	1.16	3.44
	(95%CI)	(832.1, 1,231.5)	(717.0, 1,057.6)	(240.9, 360.1)	(0.88, 1.53)	(2.60, 4.55)

Note: T: Inlive® group of 36-71 months, C1: Positive control group of 36-71 months, C2: Inlive® 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.

Safety data please see **Adverse Reactions.**
By using recipients' serum samples collected 1 month after immunization, a cross-neutralization test was conducted on 20 EV71 virus strains from 7 sub-genotypes including A (BrCr strain), C2, C4, C5, B3, B4 and B5. The results showed that the antibodies induced by Inlive® were capable to cross-neutralize other EV71 sub-genotypes.

[Package] Box, 1 Prefilled syringe @ 0.5 mL. The package unit is one syringe.

[Shelf Life] 36 months.

[Specification] Approved specification (YBS00332015) for manufacturing and testing

[Authorization Number]

Reg. No. DKI2557300443A1

HARUS DENGAN RESEP DOKTER

MEDICAL PRESCRIPTION ONLY

Store at temperature between 2°C - 8°C， protect from light.

Manufactured by:

SINOVAC BIOTECH CO., LTD.

Beijing, China

Imported by:

PT Kalventis Sinergi Farma

Jakarta, Indonesia

First approval date in Indonesia: 17 November 2022

Based on BPOM approval dated XXX – Age Extension & Standar Informasi Obat