NAME OF THE MEDICINE

IMOJEV®
Powder and diluent* for suspension for injection
Japanese encephalitis vaccine (live, attenuated)
* 0.4 % Sterile Sodium chloride solution

DESCRIPTION

IMOJEV® is a monovalent, live attenuated viral vaccine. The virus was obtained *via* recombinant DNA technology. It is based on the 17D-204 yellow fever vaccine virus in which two genes have been replaced by the corresponding genes from Japanese encephalitis (JE) virus. These are the premembrane (prM) and envelope (E) coding sequences of the SA14-14-2 live attenuated JE vaccine virus. The immunizing antigens are the prM and E proteins from the SA14-14-2 vaccine virus.

After Reconstitution:

Active Ingredients:

Live, attenuated, recombinant Japanese encephalitis virus*: 4.0 - 5.8 log PFU**
* Propagated in Vero cells
** Plaque Forming Unit

Excipients:

- Mannitol
- Lactose
- Glutamic acid
- Potassium hydroxide
- Histidine
- Human Serum Albumin
- Sodium chloride
- Water for injections

No adjuvant or antimicrobial preservative is added.

The powder is a white to creamy white homogeneous cake which might be retracted from the sides of the vial. The diluent is a clear solution. After reconstitution, **IMOJEV®** is a colourless to amber suspension.

PHARMACOLOGY

Mechanism of Action

The vaccine is a live attenuated virus. Following administration, the virus replicates locally and elicits neutralising antibodies and cell-mediated immune responses that are specific to the Japanese encephalitis (JE) virus. Available results indicate that protection is mainly mediated by neutralising antibodies.

In nonclinical studies, all animals that received a single dose of the vaccine developed specific neutralising antibodies against JE virus and were protected against infection by a virulent JE virus experimental challenge.

CLINICAL TRIALS

Immunogenicity

Passive antibody transfer results in a small animal model indicate that protection is mediated by neutralizing antibodies and that the threshold for protection is a plaque reduction neutralization titre of 1: 10.

Immunogenicity Data in Adult Populations

A single dose administration of **IMOJEV®** is as immunogenic as a three-dose regimen of an inactivated Japanese encephalitis (JE) comparator vaccine administered in adults 18 years of age and over.

A seroprotective level of antibodies is generally reached 14 days after vaccination.

In a randomized comparative Phase III trial, 410 individuals over 18 years of age received a single dose of not less than 4.0 log PFU/ dose of 0.5 mL of **IMOJEV®** and 410 individuals over 18 years of age received a three-dose regimen of 1 mL of an inactivated JE comparator vaccine.

Thirty days after vaccination, the seroprotection rates for the individuals who received **IMOJEV®** were approximately 99% when measured against the homologous virus strain. These results are non-inferior to those observed after the three-dose regimen of the inactivated JE comparator vaccine.

Fourteen days after a single dose of **IMOJEV®**, approximately 93% of the vaccinees showed seroprotective levels of neutralizing antibodies.

Table 1 shows the seroprotection rates measured against the homologous virus strain, 14 and 30 days after vaccination with a single dose of **IMOJEV®** or a three-dose regimen of the inactivated JE comparator vaccine.

Table 1: Seroprotection Rates to Homologous Virus Strain, 14 and 30 Days after the Administration of IMOJEV® or of the Inactivated JE Comparator Vaccine

Days post last-immunisation	14 days		30 days	
	IMOJEV®	Inactivated Japanese encephalitis comparator vaccine	IMOJEV®	Inactivated Japanese encephalitis comparator vaccine
Seroprotection*†	93.6% (90.5; 96.0)	-‡	99.1% (97.5; 99.8)	74.8% (70.0; 79.2)

* Based on homologous virus strain
† Seroprotection refers to neutralizing antibody titre above the threshold of protection
‡ Not applicable

Neutralising antibody levels were also assessed against a panel of wild-type strains belonging to the four main genotypes and originating from different countries. In a Phase II trial, approximately 89% of vaccinees showed neutralizing antibody levels above the 1:10 threshold against the tested wild-type strains, 28 days after a single dose administration of **IMOJEV®**.

In a long-term follow-up assessment in a randomized control phase II trial, 97.6% (95% CI, 93.3; 98.8) of individuals showed seroprotective levels six months after a single administration of **IMOJEV®**. The probability of being still seroprotected 60 months after vaccination for those who were seroprotected at six months is 86.8%.

Long-term immunogenicity data up to Month 60 are presented as Kaplan Meier estimates in Table 2.

Table 2: Long-Term Immunogenicity after a Single Dose of IMOJEV®

Visit time point	N seropositive	N seronegative	N Censored*	Kaplan-Meier estimate	95% confidence interval
Month 6	90	0	11	100.0%	100.0; 100.0
Month 12	79	2	8	97.5%	94.0; 100.0
Month 24	69	3	11	93.2%	87.5; 99.0
Month 36	55	1	6	91.5%	85.0; 98.1
Month 48	48	1	15	89.6%	82.2; 97.0
Month 60	32	1	31	86.8%	77.9; 95.8

* Individuals who were lost to follow-up were censored

No long-term immunogenicity data beyond 5 years after the administration of a single dose of **IMOJEV®** are available.

Immunogenicity Data in Paediatric Populations

- Primary Vaccination
  - o Immune response 28 days after a single dose administration of **IMOJEV®**

A seroprotective level of antibodies is generally reached 28 days after vaccination.

A single dose administration of **IMOJEV®** in 2 randomized trials in 1,231 toddlers (12 to 24 months) not previously immunized with a Japanese Encephalitis (JE) vaccine showed that approximately 95% of individuals seroconverted and were seroprotected (neutralising antibody level above the threshold of protection) after 28 days.

Table 3 shows the immune response against the homologous virus strain, 28 days after vaccination with a single dose of **IMOJEV®**.

Table 3: Immune Response 28 Days after a Single-Dose of IMOJEV® in Toddlers (12 to 24 Months) Not Previously Immunized with a JE Vaccine

	28 days post IMOJEV®-vaccination	
		95% confidence interval
Seroprotection*†	95.2%	93.9; 96.4
Seroconversion*‡	95.4%	94.0; 96.5
Geometric Mean Titre*(1/dil)	201	184; 221

* Based on homologous virus strain
† Seroprotection refers to neutralising antibody titre above the threshold of protection
‡ Seroconversion refers to:

- In individuals who are seronegative at baseline: neutralising antibody titre above the threshold of protection after vaccination with **IMOJEV®**
- In individuals who are seropositive at baseline: at least a fourfold rise in neutralising antibody titre after vaccination with **IMOJEV®**

In addition, approximately 96% of a subset of toddlers not previously immunized with a JE vaccine in a Phase II trial seroconverted to three of the four tested JE wild-type strains 28 days after a single dose administration of **IMOJEV®**, and approximately 70% seroconverted to the fourth strain.

A single dose administration of **IMOJEV®** in a randomized comparative Phase III trial in infants and toddlers (9 to 18 months) *(N = 126)* not previously immunized with a JE vaccine showed more than 99% of individuals seroconverted and were seroprotected after 28 days. These results were non-inferior to those observed after the administration of a live attenuated Japanese encephalitis comparator vaccine.

Table 4: Immune Response 28 Days, after a Single Dose of IMOJEV® or of a Live Attenuated JE Comparator Vaccine in Infants and Toddlers (9 to 18 Months) not Previously Immunized with a JE Vaccine

	IMOJEV® (N = 126)	Live attenuated Japanese encephalitis comparator vaccine (N = 128)
Seroprotection *† (95% confidence interval)	99.2% (95.7; 100.0)	99.2% (95.7; 100.0)
Geometric Mean Titre* 1/dil (95% confidence interval)	491 (378; 638)	395 (304; 514)

* Based on homologous virus strain
† "Seroprotection" refers to neutralising antibody titre above the threshold of protection

  - o Immune response up to 5 years after a single dose administration of **IMOJEV®**

The persistence of seroprotection was assessed in a Phase II and a Phase III trials in toddlers.

In the Phase II trial, approximately 59% of toddlers who did not receive any JE vaccine before the single dose administration of **IMOJEV®** were shown to still have seroprotective antibody levels 5 years after the vaccination.

Table 5 shows the immune response up to 5 years after vaccination with a single dose of **IMOJEV®**.

Table 5: Immune Response up to 5 years after a Single Dose of IMOJEV® in Toddlers (12 to 24 Months) Not Previously Immunized with a JE Vaccine

	Seroprotection* (≥ 10 1/dil) % (95% CI)	GMT* 1/dil (95% CI)
28 days after a single dose of IMOJEV® (N = 194)	96.4 (92.7; 98.5) †	295.8 (231.6; 377.9) †
6 months after a single dose of IMOJEV® (N = 197)	85.8 (80.1; 90.3) ǂ	68.5 (55.0; 85.4) ǂ
1 year after a single dose of IMOJEV® (N = 186)	79.0 (72.5; 84.6) ǂ	54.9 (43.3; 69.6) ǂ
2 years after a single dose of IMOJEV® (N = 176)	71.6 (64.3; 78.1) ǂ	57.0 (43.3; 75.1) ǂ
3 years after a single dose of IMOJEV® (N = 171)	67.3 (59.7; 74.2) ǂ	47.2 (35.5; 62.8) ǂ
4 years after a single dose of IMOJEV® (N = 172)	66.3 (58.7; 73.3) ‡	44.2 (33.5; 58.4) ‡
5 years after a single dose of IMOJEV® (N = 165)	58.8 (50.9; 66.4) ‡	26.7 (20.5; 34.8) ‡

* Based on homologous virus strain
† Full analysis set
ǂ Sensitivity analysis in the Full analysis set to avoid a bias in the antibody measurement over time due to the potential discontinuations of subjects with antibody titers below the threshold of protection

In the Phase III trial, approximately 67% of toddlers who did not receive any JE vaccine before the single dose administration of **IMOJEV®** are still seroprotected 5 years after the vaccination. All the toddlers included in this trial with serological data available 28 days after the vaccination were seroprotected at this time point.
Table 6 shows the immune response against the homologous virus strain, up to 5 years after vaccination with a single dose of **IMOJEV®**.

Table 6: Immune Response up to 5 Years after a Single-Dose of IMOJEV® in Toddlers (12 to 18 Months) Not Previously Immunised with a JE Vaccine and Seroprotected 28 days after the Single-Dose

	Seroprotection* (≥ 10 1/dil) % (95% CI)	GMT* 1/dil (95% CI)
28 days after a single-dose of IMOJEV® (N = 580)	100.0 (99.4; 100.0)	253 (225; 284)
1 year after a single-dose of IMOJEV® (N = 586)	88.2 (85.3; 90.7) †	77.2 (67.7; 88.0) †
2 years after a single-dose of IMOJEV® (N = 574)	82.4 (79.0; 85.4) ǂ	66.9 (58.5; 76.5) ǂ
3 years after a single-dose of IMOJEV® (N = 563)	77.6 (73.9; 81.0) ǂ	79.6 (67.7; 93.6) ǂ
4 years after a single-dose of IMOJEV® (N = 556)	72.8 (68.9; 76.5) ǂ	53.9 (46.5; 62.4) ǂ
5 years after a single-dose of IMOJEV® (N = 552)	67.2 (63.1; 71.1) ǂ	38.8 (33.4; 45.0) ǂ

* Based on homologous virus strain
† Full analysis set (main analysis)
ǂ Sensitivity analysis to avoid a bias in the antibody measurement over time due to the potential discontinuations of subjects with antibody titres below the threshold of protection

In another Phase III trial in infants and toddlers (9 to 18 months) not previously immunized with a JE vaccine, approximately 88% of individuals were still seroprotected 1 year after the single dose administration of **IMOJEV®**.

Table 7: Immune Response 6 Months and 1 Year after a Single Dose of IMOJEV® in Infants and Toddlers (9 to 18 Months) Not Previously Immunised with a JE Vaccine

	Seroprotection *† % (95% CI)	GMT* l/dil (95% CI)
28 days after a single dose of IMOJEV® (N = 146)	99.3 (96.2; 100.0)	507 (395; 651)
6 months after a single dose of IMOJEV® (N = 145)	94.5 (89.4; 97.6)	119 (91.7; 154)
1 year after a single dose of IMOJEV® (N = 143)	88.1 (81.6; 92.9)	97.6 (74.0; 129)

* Based on homologous virus strain
† "Seroprotection" refers to neutralising antibody titre above the threshold of protection

- Booster
  - o Booster dose of **IMOJEV®** after primary vaccination with **IMOJEV®**

In a Phase III trial, a second dose (booster dose) of **IMOJEV®** was administered in children (36 to 42 months of age) (N = 340) 24 months after primary vaccination with **IMOJEV®**. A control group of children (36 to 42 months of age) (N = 39) who never received a JE vaccine, received **IMOJEV®** for the first time to characterize the primary response to **IMOJEV®**.

The Geometric Mean Titre (GMT) increased by nearly 6 fold from Day 0 to Day 7 after the administration of **IMOJEV®** in children previously vaccinated. By comparison, the GMT did not increase in the control group, thus demonstrating an anamnestic response in the booster group. The GMT increased by nearly 57 fold from Day 0 to Day 28 in the booster group.

100% of children previously vaccinated with **IMOJEV®** showed seroprotective antibody titres 28 days after the administration of the booster dose 24 months after primary vaccination.

Table 8 shows the immune response against the homologous virus strain, 7 and 28 days after administration of a booster dose of **IMOJEV®**.

Table 8: Immune Response to a Booster Dose of IMOJEV® given to Children (36 to 42 Months) 24 Months after a Single-Dose of IMOJEV® vs. Control Children (36 to 42 Months) receiving a Single Dose of IMOJEV®

Group	Parameter	D0	D7	D28
IMOJEV® primary vaccinated toddlers (N = 340)	**Seroprotection* (≥ 10 l/dil)% [95% CI]**	80.3 [75.7; 84.4]	96.2 [93.6; 98.0]	100.0 [98.9; 100.0]
	GMT* 1/dil (ratio Dx/D0) [95% CI]**	39.4 [33.7; 46.0]	231 (5.87) [191; 279]	2,242 (57.0) [1,913; 2,628]
Japanese encephalitis-vaccine naïve control group (N = 39)	**Seroprotection* (≥ 10 l/dil) % [95% CI]**	0.0 [0.0; 9.0]	15.4 [5.9; 30.5]	89.7 [75.8; 97.1]
	GMT* 1/dil (ratio Dx/D0) [95% CI]**	5.00 [5.00; 5.00]	6.41 (1.28) [5.11; 8.05]	178 (35.6) [99.7; 318]

* Based on homologous virus strain
** Calculated as the ratio of GMTs where Dx = D7 or D28

In a Phase III trial, a second dose (booster dose) of **IMOJEV®** was administered in children (2 to 4 years of age) (N = 97) between 12 and 24 months after primary vaccination with **IMOJEV®**.

The GMT increased by nearly 51 fold from Day 0 to Day 28 in the booster group.

100% of children previously vaccinated with **IMOJEV®** showed seroprotective antibody titres 28 days after the administration of the booster dose between 12 and 24 months after primary vaccination.

Table 9: Immune Response 28 Days after the Administration of a Booster Dose of IMOJEV® in Children (2 to 4 Years) between 12 and 24 Months after a Single Dose of IMOJEV®

Group	Parameter	D0	D28
IMOJEV® primary vaccinated toddlers (N = 97)	**Seroprotection* (≥ 10 l/dil)% [95% CI]**	92.8 [85.7; 97.0]	100.0 [96.3; 100.0]
	GMT* 1/dil (ratio Dx/D0) [95% CI]**	159 [112; 226]	8,147 - (51.3) [6,702; 9,903]

* Based on homologous virus strain
** Calculated as the ratio of GMTs where Dx = D28

In the long-term follow-up assessment of the phase III trial, nearly all children (98.2%) who received the booster dose of **IMOJEV®** 24 months after primary vaccination are still seroprotected 4 years after the vaccination.

Table 10 shows the immune response up to 4 years after vaccination with a booster dose of **IMOJEV®**.

Table 10: Immune Response Up to 4 Years after the Administration of a Booster Dose of IMOJEV® in Children (36 to 42 Months) 24 Months after a Single-Dose of IMOJEV®

Group	Seroprotection* (≥ 10 l/dil) % (95% CI)	GMT* (l/dil) (95% CI)
28 days after a booster dose of IMOJEV® (N = 345)	100.0 [98.9; 100.0]	2,259 (1,930; 2,645)
1 year after a booster dose of IMOJEV® (N = 339)	99.4 (97.9; 99.9)	596 (502; 708)
2 years after a booster dose of IMOJEV® (N = 340)	98.8 (97.0; 99.7)	368 (313; 432)
3 years after a booster dose of IMOJEV® (N = 338)	99.1 (97.4; 99.8)	301 (257; 352)
4 years after a booster dose of IMOJEV® (N = 335)	98.2 (96.1; 99.3)	249 (215; 289)

* Based on homologous virus strain

  - o Booster vaccination with **IMOJEV®** after the administration of an inactivated JE vaccine as a primary immunization.

In a Phase II trial, **IMOJEV®** was administered to children (N = 97) (2 to 5 years) 6 to 38 months after a two-dose primary vaccination with an inactivated JE vaccine (mouse brain-derived JE
The GMT increased by nearly 59 fold from Day 0 to Day 28.

Approximately 93% of individuals seroconverted and they were all seroprotected (titre above a threshold considered as protective) 28 days after the administration of **IMOJEV®**.

Table 11 shows the immune response 28 days after the administration of a booster dose of **IMOJEV®** after a primary vaccination with an inactivated JE vaccine.

Table 11: Immune Response 28 Days after the Administration of a Booster Dose of IMOJEV® in Children (2 to 5 Years) 6 to 38 Months after a Two-dose Primary Vaccination with an Inactivated JE Vaccine

	D0	D28
Seroprotection*† % [95% CI]	85.6 [77.0; 91.9]	100.0 [96.3; 100.0]
Seroconversion*‡ % [95% CI]	-	92.8 [85.7; 97.0]
GMT* l/dil (ratio Dx/D0) [95% CI]**	44.8 [33.8; 59.4]	2,634 (58.7) [1,928; 3600]

* Based on homologous virus strain
** Calculated as the ratio of GMTs where Dx = D28
† Seroprotection refers to neutralising antibody titre above the threshold of protection
‡ Seroconversion refers to:
- In individuals previously immunized and who are seronegative at baseline: neutralising antibody titre above the threshold of protection after vaccination with **IMOJEV®**
- In individuals who are seropositive at baseline; at least a fourfold rise in neutralising antibody titre after vaccination with **IMOJEV®**

In addition, approximately 99% of children showed seroprotective antibody levels against JE wild-type strains belonging to the four main genotypes, 28 days after the administration of **IMOJEV®**.

In the long-term follow-up assessment of the phase II trial, nearly all children (96.3%) who received the booster dose of **IMOJEV®** 6 to 38 months after the two-dose primary vaccination with the inactivated JE vaccine are still seroprotected 5 years after the vaccination.

Table 12 shows the immune response up to 5 years after the administration of a booster dose of **IMOJEV®** after a primary vaccination with an inactivated JE vaccine.

Table 12: Immune Response up to 5 Years after the Administration of a Booster Dose of IMOJEV® in Children (2 to 5 Years) 6 to 38 Months after a Two-dose Primary Vaccination with an Inactivated JE Vaccine

	Seroprotection* (≥ 10 l/dil) % (95% CI)	GMT* l/dil (95% CI)
6 months after the administration of IMOJEV® (N = 97)	100.0 (96.3; 100.0) †	1,055.4 (771.4; 1,444.0) †
1 year after the administration of IMOJEV® (N = 93)	96.8 (90.9; 99.3) ‡	454 (327; 632) ‡
2 years after the administration of IMOJEV® (N = 84)	96.4 (89.9; 99.3) ‡	508 (351; 734) ‡
3 years after the administration of IMOJEV® (N = 81)	96.3 (89.6; 99.2) ‡	390 (278; 546) ‡
4 years after the administration of IMOJEV® (N = 80)	96.3 (89.4; 99.2) ‡	374 (249; 562) ‡
5 years after the administration of IMOJEV® (N = 81)	96.3 (89.6; 99.2) ‡	218 (157; 301) ‡

* Based on homologous virus strain
† Full analysis set
‡ Sensitivity analysis in the Full analysis set to avoid a bias in the antibody measurement over time due to the potential discontinuations of subjects with antibody titers below the threshold of protection

INDICATIONS

IMOJEV® is indicated for prophylaxis of Japanese encephalitis caused by the Japanese encephalitis virus, in individuals from 9 months of age and over.

CONTRAINDICATIONS

IMOJEV® should not be administered to anyone with a history of severe allergic reaction to any component of the vaccine or after previous administration of the vaccine or a vaccine containing the same components or constituents.

Vaccination must be postponed in case of febrile or acute disease.

Congenital or acquired immune deficiency impairing cellular immunity, including immunosuppressive therapies such as chemotherapy, high doses of systemic corticosteroids given for 14 days or more.

IMOJEV® must not be administered to individuals with symptomatic HIV infection or with asymptomatic HIV infection when accompanied by evidence of impaired immune function.

IMOJEV® must not be administered to pregnant women (see Section "Use in Pregnancy").

IMOJEV® must not be administered to breast feeding women (see Section "Use in Lactation").

PRECAUTIONS

Before the injection of any biological, the person responsible for administration must take all precautions known for the prevention of allergic or any other reactions. As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following administration of the vaccine.

In individuals who have a history of serious or severe reaction within 48 hours of a previous injection with a vaccine containing similar components, the course of the vaccination must be carefully considered.

IMOJEV® should under no circumstances be administered intravascularly.

Protection

As with any vaccine, vaccination with **IMOJEV®** may not protect 100% of vaccinated individuals.

Special Patient Groups

For patients following a treatment with high doses of systemic corticosteroids given for 14 days or more, it is advisable to wait for at least one month or more following the interruption of therapy before carrying out the vaccination until immune function has recovered.

Effects on Fertility

A reproductive and developmental toxicity study in which female rabbits were subcutaneously administered the human dose of **IMOJEV®** twice prior to mating showed no effects on female mating or fertility. No fertility data are available in humans.

Use in Pregnancy (Category B2)

Developmental toxicity studies in which female rabbits were subcutaneously administered the human dose of **IMOJEV®** twice prior to mating and three times during gestation, or once between gestation days 6 to 18, or once on postnatal day 15, showed no adverse effects on pregnancy, embryo-fetal development, parturition or postnatal development. Vaccine antigen-specific antibodies were transferred to fetuses.

As with all live attenuated vaccines, pregnancy constitutes a contraindication (see Section "Contraindications").

There is a theoretical risk that a live vaccine virus can cross the placenta and infect the fetus. It is not known whether **IMOJEV®** can cause fetal harm when administered to a pregnant woman.

Women of childbearing age should be advised not to become pregnant for 4 weeks after vaccination.

Use in Lactation

A developmental toxicity study in which female rabbits were subcutaneously administered the human dose of **IMOJEV®** once between gestation days 6 to 18, or once on postnatal day 15, showed no effects on pup survival, growth and development.

It is not known whether this vaccine is excreted in human milk.

IMOJEV® vaccination is contraindicated in breastfeeding women (see section "Contraindications").

Studies with some other live, attenuated virus vaccines have shown that a lactating postpartum woman may secrete the virus in breast milk and transmit virus to a breast-fed infant.

Paediatric Use

IMOJEV® is not recommended in children below the age of 9 months.

Use in the Elderly

In clinical trials, the seroconversion rates and the safety profiles were similar in elderly and adults after the administration of one dose of **IMOJEV®**.

Genotoxicity

IMOJEV® has not been tested for genotoxic potential.

Carcinogenicity

IMOJEV® has not been tested for carcinogenic potential.

Effect on Laboratory Tests

Interference of **IMOJEV®** with laboratory and/or diagnostic tests has not been studied.

INTERACTIONS WITH OTHER MEDICINES

Concomitant Administration with Other Vaccine(s)

Separate injection sites and separate syringes should be used when other vaccines are concomitantly administered with **IMOJEV®** (see Section "Dosage and Administration").

- From 12 months of age, **IMOJEV®** may be administered at the same time as vaccines against measles, mumps, or rubella, either stand alone or combined.
- For children living in or travelling to areas where risk for measles is high, **IMOJEV®** may be administered at the same time as measles vaccine, either stand alone or combined with mumps and/or rubella vaccines, from as early as 9 months of age.
- **IMOJEV®** may be administered to adults at the same time as the yellow fever vaccine.

Vaccine-drug Interactions

- In the case of immunosuppressive therapy or corticosteroid therapy, refer to Sections "Contraindications" and "Precautions".
- Administering the vaccine in individuals who have previously received immunoglobulins:

In order to avoid any neutralisation of the attenuated viruses contained in the vaccine, vaccination must not be performed within 6 weeks, and preferably not within 3 months of injection of immunoglobulins or blood products containing immunoglobulins, such as blood or plasma.

ADVERSE EFFECTS

Clinical Trials Experience

Data in Adult Populations

The safety of **IMOJEV®** has been assessed in 8 randomised clinical trials in individuals over 18 years of age. During the development in the adult population, approximately 2,500 individuals received an injection of **IMOJEV®.**

Safety evaluation was performed for all individuals during the first 4 weeks following vaccination and serious adverse reactions were collected during at least six months of follow-up after a single dose of **IMOJEV®**.

The most frequently reported systemic reactions after the administration of **IMOJEV®** vaccine were headache, fatigue, malaise and myalgia. All these reactions were as frequently reported as after the administration of the inactivated Japanese Encephalitis (JE) comparator vaccine or a placebo.

The most frequently reported reaction at the injection site after the administration of **IMOJEV®** vaccine was injection site pain. All the injection site reactions were less frequently reported than after the administration of the inactivated JE comparator vaccine and as frequently reported as after the administration of a placebo.

Local and systemic reactions are ranked within each system organ class, under headings of frequency, using the following convention [Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), including isolated reports].

The following possibly related Adverse Events were reported during clinical trials within 30 days after vaccination:

General Disorders and Administration Site Conditions:

- Very common: Fatigue, malaise, injection site pain
- Common: Feeling hot, chills, injection site erythema, injection site pruritus, injection site swelling, injection site bruising
- Uncommon: Pyrexia

Nervous System Disorders:

- Very common: Headache
- Common: Dizziness

Musculoskeletal and Connective Tissue Disorders:

- Very common: Myalgia
- Common: Arthralgia

Gastrointestinal Disorders:

- Common: Diarrhoea, nausea, abdominal pain, vomiting

Respiratory, Thoracic and Mediastinal Disorders:

- Common: Pharyngolaryngeal pain, dyspnea, rhinorrhea, cough, wheezing, nasal congestion

Skin and Subcutaneous Tissue Disorders:

- Common: Rash

Infections and Infestations:

- Rare: Viral infections

Table 13 below summarises the possibly related Adverse Events (frequency ≥ 1.0%) that were reported during clinical trials within 30 days after the administration of a single dose of **IMOJEV®**, of the two first doses and the third dose of the inactivated JE comparator vaccine and of the placebo doses.

Table 13: Possibly Related Adverse Events (≥ 1.0%) Reported Within 30 Days After the Administration of IMOJEV®, of the Inactivated JE Comparator Vaccine and of the Placebo

Adverse events	IMOJEV® (N = 2046)	Inactivated Japanese encephalitis comparator vaccine Dose 1 and 2 (N = 440)	Inactivated Japanese encephalitis comparator vaccine Dose 3 (N = 422)	Placebo Dose 1 and 2 (N = 440)	Placebo (N = 435)
General disorders and administration site conditions					
Fatigue	21.0%	23.6%	10.9%	26.6%	22.1%
Malaise	17.0%	20.5%	9.0%	17.5%	16.3%
Injection site pain	11.8%	58.4%	34.8%	20.2%	9.2%
Feeling hot	8.4%	7.3%	4.7%	8.2%	6.9%
Chills	6.0%	5.5%	1.9%	7.3%	4.1%
Injection site erythema	4.4%	24.8%	17.5%	3.4%	3.2%
Injection site pruritus	3.6%	19.5%	12.6%	5.0%	2.5%
Injection site swelling	1.3%	13.9%	12.6%	1.6%	0.9%
Injection site bruising	1.1%	3.2%	1.4%	2.5%	1.1%
Pyrexia	0.9%	1.1%	1.2%	1.1%	1.4%
Nervous system disorders					
Headache	23.9%	32.5%	15.6%	30.7%	24.6%
Dizziness	1.1%	0.9%	0.2%	0.5%	0.7%
Musculoskeletal and connective tissue disorders					
Myalgia	14.7%	17.5%	6.9%	15.7%	11.5%
Arthralgia	6.6%	8.6%	3.8%	8.6%	4.6%
Gastrointestinal disorders					
Diarrhoea	7.6%	7.3%	2.4%	7.0%	5.7%
Nausea	6.5%	8.4%	4.3%	5.9%	6.4%
Abdominal pain	5.1%	5.7%	3.3%	8.0%	4.8%
Vomiting	1.0%	1.1%	0.9%	1.4%	1.6%
Respiratory, thoracic and mediastinal disorders					
Pharyngolaryngeal pain	2.9%	2.3%	1.2%	2.3%	2.3%
Dyspnea	2.7%	3.2%	1.4%	3.0%	2.3%
Rhinorrhoea	1.5%	0.5%	0.0%	0.5%	2.1%
Cough	1.4%	0.9%	0.9%	0.9%	1.8%
Wheezing	1.3%	1.4%	0.2%	2.3%	1.8%
Nasal congestion	1.0%	0.7%	0.7%	0.2%	2.1%
Skin and subcutaneous tissue disorders					
Rash	1.2%	3.9%	2.1%	2.3%	1.8%

Data in Paediatric Populations

The safety of **IMOJEV®** in paediatric populations has been assessed in Phase II and Phase III clinical trials. Overall, approximately 2,200 children received at least one injection of **IMOJEV®** in these studies.

In addition, 10,000 individuals between 9 months and 5 years of age received **IMOJEV®** either primary or booster vaccination in a large scale Phase IV safety trial aimed at identifying serious, rare adverse reactions (see Adverse Reactions from Post-Marketing Surveillance section).

Results from 5 Phase II and Phase III clinical trials with similar methodology for recording safety data were included in an integrated analysis of safety. During these clinical trials approximately 2,200 individuals between 9 months and 5 years of age received an injection of **IMOJEV®** (approximately 50 infants from 9 to 12 months old and 2,050 toddlers from 12 months not previously immunised with a JE vaccine, as well as 100 children previously immunised with a two-dose regime of a JE vaccine).

Safety evaluation was performed for all individuals during the first 4 weeks following vaccination and serious adverse reactions were collected during at least six months of follow-up after a single dose of **IMOJEV®**.

The most frequently reported systemic reactions were malaise, myalgia, fever, and headache in children (2 to 5 years); and irritability, appetite loss, crying and fever in infants and toddlers (9 to 24 months).

The most frequently reported reactions at the injection site after the administration of **IMOJEV®** vaccine was injection site pain/tenderness and injection site erythema.

These adverse events observed during paediatric clinical trials were generally of mild intensity and of short duration. The onset of systemic reactions was generally seen within 3 days after immunisation.

Table 14 below summarises the solicited reactions that were reported during clinical trials after the administration of a single dose of IMOJEV® or of a control vaccine.

Table 14: Solicited Reactions after the Administration of IMOJEV® or of a Control Vaccine (Reported Within 7 Days for Injection Site Reactions and 14 Days for Systemic Reactions)

Solicited reactions	IMOJEV® (N = 2198)	Hepatitis A (N = 400)
Injection site reaction		
Injection site pain/tenderness	22.4%	25.1%
Injection site erythema	19.7%	20.6%
Injection site swelling	6.0%	7.8%
Systemic reactions		
Fever	20.2%	18.8%
Headache	21.0%	14.3%
Malaise	33.0%	26.5%
Myalgia	24.0%	15.3%
Vomiting	16.8%	19.9%
Inconsolable crying	20.4%	19.9%
Drowsiness	19.0%	16.6%
Appetite lost	25.4%	28.2%
Irritability	27.1%	24.6%

Table 15 below summarises the non-serious adverse reactions that were reported during clinical trials within 28 days after the administration of a single dose of **IMOJEV®** or of a control vaccine.

Table 15: Unsolicited Non-serious Adverse Reactions within 28 days after the Administration of IMOJEV® or of a Control Vaccine

Unsolicited Non-serious Adverse Reactions	IMOJEV® (N = 2198)	Hepatitis A (N = 400)
General disorders and administration site conditions		
Injection site bruising	0.3%	0.3%
Injection site haematoma	0.2%	0.0%
Injection site haemorrhage	0.2%	0.0%
Injection site induration	0.1%	0.0%
Injection site pruritus	< 0.1%	0.0%
Gastrointestinal disorders		
Vomiting	0.1%	0.0%
Infections and infestations		
Upper respiratory tract infection	0.1%	0.0%
Viral infection	< 0.1%	0.0%
Skin and subcutaneous tissue disorders		
Post inflammatory pigmentation change	< 0.1%	0.0%
Rash	< 0.1%	0.0%
Rash maculo-papular	< 0.1%	0.3%
Urticaria	0.1%	0.0%

Local and systemic reactions are ranked within each system organ class, under headings of frequency, using the following convention [Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), including isolated reports].

The following related Adverse Events were reported during clinical trials within 28 days after vaccination:

General Disorders and Administration Site Conditions:

- Very common: Pyrexia, malaise, irritability, injection site pain/tenderness, injection site erythema
- Common: Injection site swelling
- Uncommon: Injection site reactions (induration, bruising, haematoma, haemorrhage)
- Rare: Injection site pruritus

Nervous System Disorders:

- Very common: Headache, somnolence

Musculoskeletal and Connective Tissue Disorders:

- Very common: Myalgia

Gastrointestinal Disorders:

- Very common: Vomiting

Metabolism and Nutrition Disorders:

- Very common: Appetite loss

Infections and infestations:

- Uncommon: Upper respiratory tract infection
- Rare: Viral infection

Skin and Subcutaneous Tissue Disorders:

- Uncommon: Urticaria
- Rare: Rash, maculo-papular rash, post inflammatory pigmentation change

Psychiatric Disorders:

- Very common: Inconsolable crying

No serious adverse events within 28 days of administration of **IMOJEV®** were related to vaccination.

During the paediatric clinical trials, 29 cases of convulsions have been reported, including 28 cases of febrile convulsion and 1 case of convulsion without fever. All cases were assessed as not related to vaccination and were reported to be associated with concurrent infectious diseases (or common cold). In 9 cases, convulsions started within 30 days after **IMOJEV®** vaccination.

In the following studies, the safety of **IMOJEV®** presented no clinically relevant difference with the above-described safety profile:

- In a Phase III trial in 390 individuals between 36 and 42 months of age (45 out of the 390 received a single dose of **IMOJEV®**, and 345 out of the 390 received a second dose (booster dose) of **IMOJEV®** 2 years after the first dose).
- In a Phase III trial in 119 children between 18 and 36 months of age who received a second dose (booster dose) of **IMOJEV®**.

Adverse Reactions from Post-Marketing Surveillance

No additional adverse reactions were identified from the Phase IV safety trial conducted in 10,000 individuals between 9 months and 5 years of age, as well as from spontaneous reporting in post-marketing surveillance.

DOSAGE AND ADMINISTRATION

Primary Vaccination:

Individuals 9 months of age and over: a 0.5 mL single injection of the reconstituted vaccine.

Booster:

- Adult population (18 years of age and over)

There is no need for a booster dose up to 5 years after the administration of a single dose of **IMOJEV®**.

- Paediatric population (9 months to 17 years of age inclusive)

A booster dose of **IMOJEV®** should be given after primary vaccination in order to confer long term protection. The booster dose should be given preferably 12 months after primary vaccination and can be given up to 24 months after primary vaccination.

IMOJEV® can also be given as a booster vaccination in children who were previously given an inactivated Japanese Encephalitis (JE) vaccine for primary vaccination, in accordance with the recommended timing for the booster of the inactivated JE vaccine.

Safety and efficacy of a booster dose in children and adolescents 5 to 17 years of age have not been established. Nevertheless, the booster dose can be considered based on the available data in other age groups.

Once the freeze-dried vaccine has been completely reconstituted using the diluent provided (see Section "Instructions for Use"), it is administered *via* the subcutaneous route.

In individuals 2 years of age and over, the recommended injection site is the deltoid region of the upper arm.

In individuals between 9 and 24 months of age, the recommended injection site is the anterolateral aspect of the thigh or the deltoid region.

Do not administer by intravascular injection.

IMOJEV® must not be mixed with any other injectable vaccine(s) or medicinal product(s).

Contact with disinfectants is to be avoided since they may inactivate the vaccine virus.

Product is for single use in one patient only. Discard any residue.

Instructions for Use

Using aseptic technique, **IMOJEV®** vaccine is reconstituted by injecting all the 0.4 % sodium chloride solution into the vial of freeze-dried vaccine, using the syringe and one of the needles provided in the carton. The vial is gently swirled. After complete dissolution, a 0.5 mL dose of the reconstituted suspension is withdrawn into this same syringe. For injection, the syringe is fitted with the second needle provided in the package.

The product should be used once reconstituted and must be discarded if it is not used within one hour of reconstitution.

After use, any remaining vaccine and container must be disposed of safely, preferably by heat inactivation or incineration, according to locally agreed procedures.

OVERDOSE

There is no specific information regarding overdose with **IMOJEV®**.

PRESENTATION AND STORAGE CONDITIONS

One dose of freeze-dried vaccine and one dose of diluent in separate vials (type I glass), each equipped with a stopper (halo-butyl) and a flip off cap (aluminium/polypropylene), with one syringe (polypropylene) and two needles (stainless steel). Pack size of 1 powder vial and 1 diluent vial, 1 syringe and 2 needles.

Store in a refrigerator (2 – 8°C). Do not freeze.

Keep the vials in the outer carton in order to protect from light.

NAME AND ADDRESS OF MANUFACTURER

Manufactured by:
Global Biotech Products Co., Ltd. (For Substipharm Biologics Ltd as a product owner)

241 Moo 7 Gateway City Industrial Estate, Huasamrong, Plaengyao, Chachoengsao 24190 Thailand

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