AUSTRALIAN PRODUCT INFORMATION

NAME OF THE MEDICINE

IMOJEV®

Japanese encephalitis vaccine (live, attenuated)

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 It is based on the 17D-204 yellow fever vaccine virus in which two genes have been replaced by the corresponding genes from Japanese encephalitis (JE) virus.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 immunising 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 neutralising antibodies and that the threshold for protection is a plaque reduction neutralisation 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 randomised 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 neutralising 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* † (%) (95% confidence interval)	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 neutralising 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 neutralising 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 randomised 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
Months 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
    - 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 randomised trials in 1,231 toddlers (12 to 24 months) previously not immunised with a Japanese encephalitis (JE) vaccine showed that approximately 95% of individuals seroconverted and were seroprotected (neutralising antibody level above the threshold of protection).

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 Immunised 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 previously not immunised 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.

- Immune response up to 3 years after a single dose administration of IMOJEV

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

In the Phase II trial, approximately 75% of toddlers who did not receive any JE vaccine before the single dose administration of IMOJEV were shown to still have seroprotective antibody levels 3 years after the vaccination.

Table 4 shows the immune response up to 3 years after vaccination with a single dose of IMOJEV.

Table 4: Immune Response up to 3 Years after a Single-Dose of IMOJEV in Toddlers (12 to 24 Months) Not Previously Immunised 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)	86.8 (81.3; 91.2) †	69.5 (55.9; 86.4) †
1 year after a single dose of IMOJEV (N=185)	82.2 (75.9; 87.4) ‡	58.2 (46.2; 73.3) ‡
2 years after a single dose of IMOJEV (N=172)	80.2 (73.5; 85.9) ‡	70.3 (54.3; 91.1) ‡
3 years after a single dose of IMOJEV (N=157)	75.2 (67.6; 81.7) ‡	60.6 (45.5; 80.7) ‡

* 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 titres below the threshold of protection

No clinical trial data on persistence of seroprotection beyond 3 years after the administration of a single dose of IMOJEV are available.

In the phase III trial, approximately 86% of toddlers who did not receive any JE vaccine before the single dose administration of IMOJEV are still seroprotected 2 years after the vaccination. All the toddlers included in this trial with serological data available 28 days after the vaccination were seroprotected at this timepoint.

Table 5 shows the immune response against the homologous virus strain, up to 2 years after vaccination with a single dose of IMOJEV.

Table 5: Immune Response up to 2 Years after a Single-Dose of IMOJEV in Toddlers (12 to 24 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)	85.9 (82.8; 88.6) ‡	71.4 (62.7; 81.3) ‡

* Based on homologous virus strain

† Full analysis set (main analysis)

‡ 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

- Booster
    - 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) (N=340) 24 months after primary vaccination with IMOJEV. A control group of children (36 to 42 months) (N=39) who never received a JE vaccine, received IMOJEV for the first time to characterise 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.

Table 6 shows the immune response against the homologous virus strain, 7 and 28 days after administration of a booster dose of IMOJEV.

Table 6: 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 1/dil) % [95%CI]**	80.3 [75.7; 84.4]	96.2 [93.6; 97.9]	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 1/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

In the long-term follow-up assessment of the phase III trial, nearly all children (99.4%) who received the booster dose of IMOJEV 24 months after primary vaccination are still seroprotected 1 year after the vaccination.

Table 7 shows the immune response 28 days and 1 year after vaccination with a booster dose of IMOJEV.

Table 7: Immune Response 28 Days and 1 Year after the Administration of a Booster Dose of IMOJEV in Children (36 to 42 Months) 24 Months after a Single-Dose of IMOJEV

	Seroprotection* (≥ 10 1/dil) % (95% CI)	**GMT* (1/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)

* Based on homologous virus strain

- Booster vaccination with IMOJEV after the administration of an inactivated JE vaccine as a primary immunisation

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 vaccine).

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 8 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 8: Immune Response 28 Days after the Administration of a Booster Dose of IMOJEV in Children (2 to 5 Years) 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* **1/dil (ratio Dx/D0)** **[95%CI]**	44.8 [33.8; 59.4]	2,634 (58.7) [1,928; 3,600]

* Based on homologous virus strain

† Seroprotection refers to neutralising antibody titre above the threshold of protection

‡ Seroconversion refers to:

- In individuals previously immunised 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 (97.5%) 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 3 years after the vaccination.

Table 9 shows the immune response up to 3 years after the administration of a booster dose of IMOJEV after a primary vaccination with an inactivated JE vaccine.

Table 9: Immune Response up to 3 Years after the Administration of a Booster Dose of IMOJEV in Children (2 to 5 Years) after a Two-dose Primary Vaccination with an Inactivated JE Vaccine

	Seroprotection* (≥10 1/dil) % (95% CI)	**GMT* 1/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)	97.6 (91.7; 99.7) ‡	521 (364; 744) ‡
3 years after the administration of IMOJEV (N=78)	97.5 (91.3;99.7) ‡	411 (298;569) ‡

* 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 titres below the threshold of protection

INDICATIONS

IMOJEV is indicated for prophylaxis of Japanese encephalitis caused by the Japanese encephalitis virus, in individuals from 12 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 generally 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 breastfeeding women (see Section “Use in Lactation”).

PRECAUTIONS

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.

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.

IMOJEV should under no circumstances be administered intravascularly.

Effects on Fertility

A reproductive and developmental toxicity study in which female rabbits were SC 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 SC 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 SC 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 infect a breast-fed infant.

Paediatric Use

IMOJEV is not recommended in children below the age of 12 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

No studies have been conducted of concomitant administration of IMOJEV and other vaccines with the exception of yellow fever vaccine in adults. In adults, IMOJEV may be administered at the same time as yellow fever vaccine using separate syringes, and into separate limbs.
In children, IMOJEV should not be administered concomitantly with other vaccines, particularly paediatric vaccines that are included in the national immunisation program.

In the case of immunosuppressive therapy or corticosteroid therapy, refer to Section "Contraindications" and “Precautions”.

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.

Table 10 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 10: 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%

The following possibly related Adverse Events (frequency < 1.0%) were reported during clinical trials within 30 days after the administration of a single dose of IMOJEV. These events were as frequently reported as after the administration of the inactivated JE comparator vaccine or the placebo:

- **General disorders and administration site conditions:** Influenza like illness, injection site rash, chest discomfort, injection site reaction, injection site induration, oedema peripheral, irritability, injection site haemorrhage, injection site warmth, injection site paraesthesia, asthenia, injection site joint pain, injection site discomfort, tenderness
- **Nervous system disorders:** Sinus headache, lethargy, paraesthesia, migraine, somnolence, syncope vasovagal, dizziness postural
- **Musculoskeletal and connective tissue disorders:** Back pain, neck pain, pain in extremity, musculoskeletal pain, pain in jaw, musculoskeletal stiffness, muscle spasms, muscle tightness, intervertebral disc compression
- **Gastrointestinal disorders:** Abdominal pain upper, dry mouth, lip swelling, dyspepsia, palatal oedema, tongue oedema
- **Infections and infestations:** Viral infection, urinary tract infection, gastroenteritis, subcutaneous abscess
- **Respiratory, thoracic and mediastinal disorders:** Sneezing, asthma, pharyngeal erythema, throat irritation
- **Skin and subcutaneous tissue disorders:** Pruritus, pruritus generalized, rash maculo-papular, rash generalised, swelling face, eczema, urticaria, rash popular, rash macular, rash erythematous
- **Investigations:** Alanine aminotransferase increased, lymph node palpable
- **Injury, poisoning and procedural complications:** Sunburn
- **Blood and lymphatic system disorders:** Lymphadenopathy, leukopenia, lymph node pain, lymphopenia
- **Psychiatric disorders:** Insomnia
- **Ear and labyrinth disorders**: Ear pain, tinnitus, vertigo
- **Eye disorders:** Eye pain, vision blurred, eye pruritus, eye swelling
- **Vascular disorders:** Flushing, hot flush, hypertension
- **Cardiac disorders:** Sinus tachycardia
- **Immune system disorders:** Hypersensitivity
- **Metabolism and nutrition disorders:** Decreased appetite, increased appetite

Data in paediatric populations

The safety of IMOJEV has been assessed in 2 randomised clinical trials in individuals between 12 months and 5 years of age. During the development in paediatric populations, approximately 1,400 individuals (100 children and 1,300 toddlers) 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 were malaise, fever, headache and myalgia in children (2 to 5 years) previously immunised with a two-dose primary vaccination with an inactivated JE vaccine; and fever, appetite lost and irritability in toddlers (12 to 24 months) not previously immunised with a JE vaccine.

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 11 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 11: 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=1396)	Hepatitis A (N=400)
Injection site reaction		
Injection site pain/tenderness	23.6%	25.1%
Injection site erythema	23.4%	20.6%
Injection site swelling	7.2%	7.8%
Systemic reactions		
Fever	20.7%	18.8%
Headache	21.0%	14.3%
Malaise	33.0%	26.5%
Myalgia	24.0%	15.3%
Vomiting	19.2%	19.9%
Crying abnormal	19.1%	19.9%
Drowsiness	18.4%	16.6%
Appetite lost	25.9%	28.2%
Irritability	28.5%	24.6%

Table 12 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 12: 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=1396)	Hepatitis A (N=400)
General disorders and administration site conditions		
Injection site bruising	0.2%	0.3%
Injection site haematoma	0.3%	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%

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

Febrile convulsions within 14 days of administration of IMOJEV were reported in three children. In all cases, febrile convulsions were not related to vaccination and were associated with concomitant infectious diseases.

The safety of IMOJEV has also been assessed in a Phase III trial in 390 children between 36 and 42 months of age (45 children received a single dose of IMOJEV, and 345 children received a second dose (booster dose) of IMOJEV 2 years after the first dose). The safety profile presented no clinically relevant difference with the safety profile described above.

Adverse Reactions from Post-Marketing Surveillance

There is no safety data from post-marketing experience with IMOJEV.

DOSAGE AND ADMINISTRATION

Primary vaccination:

Individuals 12 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

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 group.

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 12 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

No case of overdose has been reported.

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°C – 8°C). Do not freeze.

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

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG)

23 August 2010

DATE OF MOST RECENT AMENDMENT

25 November 2013