

1. NAME OF THE MEDICINAL PRODUCT

IXIARO suspension for injection
Japanese encephalitis vaccine (inactivated, adsorbed)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 ml) of IXIARO contains:
Japanese encephalitis virus strain SA₁₄₋₁₄₋₂ (inactivated)^{1,2} 6 AU³
corresponding to a potency of ≤ 460 ng ED₅₀

¹ produced in Vero cells

² adsorbed on aluminium hydroxide, hydrated (approximately 0.25 milligrams Al³⁺)

³ Antigen Units

Excipients with known effect:

This medicine contains potassium, less than 1mmol (39 mg) per 0.5 ml single dosage i.e. essentially 'potassium-free' and less than 1 mmol sodium (23 mg) per 0.5 ml single dosage, that is to say essentially 'sodium-free'. This product might contain traces of residual sodium metabisulfite which is below detection limit.

Phosphate Buffered Saline 0.0067 M (in PO₄) has the following saline composition:

NaCl – 9mg/mL

KH₂PO₄ – 0.144 mg/mL

Na₂HPO₄ – 0.795 mg/mL

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.
Clear liquid with a white precipitate.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IXIARO is indicated for active immunisation against Japanese encephalitis in adults, adolescents, children and infants aged 2 months and older.

IXIARO should be considered for use in individuals at risk of exposure through travel or in the course of their occupation.

4.2 Posology and method of administration

Posology

Adults (18 to \leq 65 years of age)

The primary vaccination series consists of two separate doses of 0.5 ml each, according to the following conventional schedule:

First dose at Day 0.

Second dose: 28 days after first dose.

Rapid schedule

Persons aged 18 to \leq 65 years can be vaccinated in a rapid schedule as follows:

First dose at Day 0.

Second dose: 7 days after first dose.

With both schedules, primary immunisation should be completed at least one week prior to potential exposure to Japanese encephalitis virus (JEV) (see section 4.4).

It is recommended that vaccinees who received the first dose of IXIARO complete the primary 2-dose vaccination course with IXIARO.

If the primary immunization of two injections is not completed, full protection against the disease might not be achieved. There is data that a second injection given up to 11 months after the first dose results in high seroconversion rates (see section 5.1).

Booster dose

A booster dose (third dose) should be given within the second year (i.e. 12 - 24 months) after primary immunization, prior to potential re-exposure to JEV.

Persons at continuous risk for acquiring Japanese encephalitis (laboratory personnel or persons residing in endemic areas) should receive a booster dose at month 12 after primary immunization (see section 5.1).

Long-term seroprotection data following a first booster dose administered 12 - 24 months after primary immunization suggest that a second booster should be given 10 years after the first booster dose, prior to potential exposure to JEV.

Elderly (>65 years of age)

The primary vaccination series consists of two separate doses of 0.5 ml each, according to the following conventional schedule:

First dose at Day 0.

Second dose: 28 days after first dose.

The primary immunisation should be completed at least one week prior to potential exposure to Japanese encephalitis virus (JEV) (see section 4.4).

It is recommended that vaccinees who received the first dose of IXIARO complete the primary 2-dose vaccination course with IXIARO.

If the primary immunization of two injections is not completed, full protection against the disease might not be achieved. There is data that a second injection given up to 11 months after the first dose results in high seroconversion rates (see section 5.1).

Booster dose

As with many vaccines, the immune response in elderly persons to IXIARO is lower than in younger adults. Duration of protection is uncertain in elderly persons, therefore a booster dose (third dose) should be considered before any further exposure to JE virus. Long-term seroprotection following a booster-dose is not known.

Paediatric Population

Children and adolescents from 3 years to < 18 years of age

The primary vaccination series consists of two separate doses of 0.5 ml according to the following schedule:

First dose at Day 0.

Second dose: 28 days after first dose.

Children from 2 months to < 3 years of age

The primary vaccination series consists of two separate doses of 0.25 ml according to the following schedule:

First dose at Day 0.

Second dose: 28 days after first dose.

See section 6.6 for instructions on preparing a 0.25 ml dose for children aged 2 months to <3 years.

It is recommended that vaccinees who received the first dose of IXIARO complete the primary 2-dose vaccination course with IXIARO.

Booster dose (Children and adolescents)

A booster dose (third dose) should be given within the second year (i.e. 12 - 24 months) after primary immunization, prior to potential re-exposure to JEV.

Children and adolescents at continuous risk for acquiring Japanese encephalitis (residing in endemic areas) should receive a booster dose at month 12 after primary immunization (see section 5.1).

Children and adolescents from 3 years to < 18 years of age should receive a single 0.5 ml booster dose.

Children from 14 months to < 3 years of age should receive a single 0.25 ml booster dose.

See section 6.6 for instructions on preparing a 0.25 ml dose for children aged 2 months to <3 years.

No long-term seroprotection data beyond two years after a first booster administered 1 year after primary immunization has been generated in children.

Children below 2 months of age

The safety and efficacy of IXIARO in children younger than 2 months has not been established. No data are available.

Method of administration

The vaccine should be administered by intramuscular injection into the deltoid muscle. In infants, the anterolateral aspect of the thigh may be used as injection site. IXIARO should never be injected intravascularly.

When IXIARO is administered concomitantly with injectable vaccines, they should be given with separate syringes at opposite sites.

Exceptionally, IXIARO can also be administered subcutaneously to patients with thrombocytopenia or bleeding disorders since bleeding may occur following an intramuscular administration. Subcutaneous administration could lead to a suboptimal response to the vaccine (see section 4.4). However, it should be noted that there are no clinical efficacy data to support administration by the subcutaneous route.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to the residues protamine sulphate, formaldehyde, bovine serum albumin, host cell DNA, sodium metabisulphite (see section 2.), host cell protein.

Individuals who show hypersensitivity reactions after receiving the first dose of the vaccine should not be given the second dose.

Administration must be postponed in persons with acute severe febrile conditions.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

As with all injectable vaccines, appropriate medical treatment and supervision should always be available to treat rare cases of anaphylactic reactions following the administration of the vaccine.

Under no circumstances should IXIARO be administered intravascularly.

As with any other vaccine, vaccination with IXIARO may not result in protection in all cases. IXIARO will not protect against encephalitis caused by other micro-organisms. Like other intramuscular injections, this vaccine should not be administered intramuscularly to persons with thrombocytopenia, haemophilia or other bleeding disorders (see section 4.2). In adults a seroconversion rate of 29.4 % has been observed 10 days after the first i.m. vaccination, and 97.3 % one week after the second i.m. vaccination in the conventional schedule. After immunisation with the rapid schedule a seroconversion rate of 99% has been observed 7 days after the second i.m. vaccination. Hence, primary immunisation should be completed at least one week prior to potential exposure to Japanese encephalitis virus (JEV). Protection against Japanese Encephalitis is not ensured until the second dose has been received.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of IXIARO with other vaccines:

Concomitant administration of IXIARO with inactivated hepatitis A vaccine and with inactivated rabies vaccine in two different schedules has been evaluated in clinical studies. There was no interference with the immune response to Japanese encephalitis virus (JEV) or to hepatitis A or rabies virus vaccines (see section 5.1).

The safety profiles of IXIARO and the other studied vaccines were not compromised when administered concomitantly.

In patients receiving immunosuppressive therapy or patients with immunodeficiency an adequate immune response may not be obtained.

Paediatric population

No interaction studies have been performed in children and adolescents.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from the use of IXIARO in pregnant women. In animal studies findings of unclear clinical relevance have been identified (see section 5.3). As a precautionary measure, the use of IXIARO during pregnancy should be avoided.

Breast-feeding

It is unknown whether IXIARO is excreted in human milk. No effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to IXIARO is negligible. However, in the absence of data and as a precautionary measure the use of IXIARO during lactation should be avoided.

Fertility

A study in rats did not indicate vaccine-related effects on female reproduction, foetal weight, survival and development of the off-spring.

4.7 Effects on ability to drive and use machines

IXIARO has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of Ixiaro was assessed in controlled and uncontrolled clinical studies in 5,021 healthy adults (from non-endemic countries) and 1,559 children and adolescents (mostly from endemic countries). Approximately 40% of treated subjects experienced systemic adverse reactions and approximately 54% experienced injection site reactions. They usually occur within the first three days after vaccination, are

usually mild and resolve within a few days. No increase in the number of adverse reactions was noted between first and second doses or following a booster dose in adults.

Most commonly reported adverse reactions in adults included headache (20% of subjects), myalgia (13%), injection site pain (33%), injection site tenderness (33%) and fatigue (12.9%).

Most commonly reported adverse reactions in children and adolescents included pyrexia, diarrhoea, influenza like illness, irritability, injection site pain, injection site tenderness, and injection site redness (see table 1).

Adverse reactions are listed according to the following frequencies:

Very common: $\geq 1/10$

Common: $\geq 1/100$ to $< 1/10$

Uncommon: $\geq 1/1,000$ to $< 1/100$

Rare: $\geq 1/10,000$ to $< 1/1,000$

Adult and older adults (>65 years) population

Blood and lymphatic system disorders

Uncommon: lymphadenopathy

Rare: thrombocytopenia

Nervous system disorders

Very common: headache

Uncommon: migraine, dizziness

Rare: paraesthesia, neuritis, dysgeusia, syncope*

Eye disorders

Rare: eyelid oedema

Ear and labyrinth disorders

Uncommon: vertigo

Cardiac disorders

Rare: palpitations, tachycardia

Respiratory, thoracic and mediastinal disorders

Rare: dyspnoea

Gastrointestinal disorders

Common: nausea

Uncommon: vomiting, diarrhoea, abdominal pain

Skin and subcutaneous tissue disorders

Uncommon: rash, pruritus, hyperhidrosis

Rare: urticaria, erythema

Musculoskeletal and connective tissue disorders

Very common: myalgia

Uncommon: musculoskeletal stiffness, arthralgia

Rare: pain in extremity

General disorders and administration site conditions

Very common: injection site pain, injection site tenderness, fatigue

Common: influenza like illness, pyrexia, other injection site reactions e.g. redness, hardening, swelling, itching

Uncommon: chills, malaise, asthenia

Rare: oedema peripheral

Investigations

Uncommon: hepatic enzymes increased

*reported also from post-marketing experience

Paediatric population (2 months to <18 years of age)

Table 1: Frequency of adverse reactions observed in children given the 0.25 ml dose (2 months to <3 years of age) and in children and adolescents given the 0.5 ml dose (3 years to <18 years of age)

System Organ Class Preferred Term	Frequency of adverse reactions(%) by dose/age	
	0.25 ml N=783 2 months to <3 years	0.5 ml N=628 3 to <18 years
Blood and Lymphatic System Disorders		
Lymphadenopathy	0.1	0.0
Metabolism and Nutrition Disorders		
Decreased appetite	8.2	1.9
Nervous System Disorders		
Headache	2.9	6.1
Respiratory, Thoracic and Medistinal Disorders		
Cough	0.5	0.3
Gastrointestinal Disorders		
Diarrhoea	11.9	1.4
Vomiting	7.3	1.9
Nausea	3.9	1.9
Abdominal pain	0.1	0.0
Skin and Subcutaneous Tissue Disorders		
Rash	6.3	1.4
Musculoskeletal and Connective Tissue Disorders		
Myalgia	3.0	7.1
General Disorders and Administration Site Conditions		
Pyrexia	28.5	10.4
Influenza like illness	10.9	2.9
Irritability	10.9	1.9
Fatigue	3.5	3.5
Injection site redness	10.0	4.1
Injection site pain	6.1	14.1
Injection site tenderness	4.2	14.7
Injection site swelling	3.6	2.2
Injection site hardening	1.2	1.9
Injection site itching	0.6	1.6
Investigations		
Hepatic enzymes increased	0.5	0.2

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 reactions via [the national reporting system listed in Appendix V](#).

4.9 Overdose

No symptoms related to overdose were reported.

Paediatric population:

No case of overdose has been reported in the paediatric population. Inadvertent administration of an 0.5 ml dose of IXIARO in children aged 1 to <3 years does not pose any safety concerns (section 5.1.).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccines, Viral vaccines, Encephalitis vaccines. ATC code: J07BA02

Mechanism of action

The mechanism of action of Japanese encephalitis (JE) vaccines is not well understood. Studies in animals have shown that the vaccine triggers the immune system to produce antibodies against Japanese encephalitis virus that are most often protective. Challenge studies were performed in mice that were treated with human IXIARO antisera. These studies showed that almost all mice that had a Plaque Reduction Neutralization Test titre of at least 1:10 were protected from a lethal Japanese encephalitis virus challenge.

Clinical efficacy and safety

No prospective efficacy trials have been performed. Immunogenicity of IXIARO was studied in approximately 3,119 healthy adult subjects included in seven randomized, controlled and five uncontrolled Phase 3 trials and in approximately 550 healthy children included in two randomized, controlled and two uncontrolled Phase 3 clinical trials.

Pivotal immunogenicity trial (adults)

Immunogenicity of the vaccine was evaluated in a randomized, active controlled, observer blinded, multicenter Phase 3 clinical trial including 867 healthy male and female subjects given IXIARO or the US licensed JEV vaccine JE VAX (on a 0, 7 and 28 day schedule by subcutaneous injection). The co-primary endpoint was seroconversion rate (anti JEV antibody titer \geq 1:10) and geometric mean titers (GMT) at Day 56 as assessed by a Plaque Reduction Neutralization Test (PRNT) for the entire study population.

By Day 56, the proportion of subjects who had seroconverted was similar for both treatment groups (96.4% vs. 93.8% for IXIARO and JE VAX, respectively). GMT increased by Day 56 to 243.6 for IXIARO and to 102.0 for JE VAX, respectively. The immune responses elicited by IXIARO were non inferior to those induced by JE VAX (Table 2).

Table 2: Seroconversion rates and geometric mean titers of IXIARO and JE VAX in the Per Protocol Population. Neutralising antibody titers against JEV were measured against the JEV strain SA₁₄₋₁₄₋₂.

Seroconversion rate		
Time point	IXIARO N=365 % (n)	JE-VAX N=370 % (n)
Visit 0 (Screening)	0	0
Visit 3 (Day 28)	54 (197)	86.8 (321)
Visit 4 (Day 56)	96.4 (352)	93.8 (347)
Geometric mean titer (by plaque reduction neutralization test)		
Time point	IXIARO N=365 GMT (n)	JE-VAX N=370 GMT (n)
Visit 0 (Screening)	5.0 (365)	5.0 (370)
Visit 3 (Day 28)	17.4 (363)	76.9 (367)
Visit 4 (Day 56)	243.6 (361)	102.0 (364)

The effect of age on the immune response to IXIARO and JE-VAX was assessed as a secondary endpoint in this active controlled study, comparing subjects aged ≥ 50 years of age (N=262, mean age 59.8) with those below 50 years of age (N=605, mean age 33.9).

There was no significant difference between seroconversion rates of IXIARO and JE-VAX in subjects aged <50 years compared to those aged ≥ 50 years at Day 28 or Day 56 following vaccination. Geometric mean titers were significantly higher at Day 28 in subjects aged <50 years than those aged ≥ 50 years in the JE VAX group (80.9 vs. 45.9, $p=0.0236$) but there was no significant difference at Day 56 for this treatment group. There were no significant effects of age on geometric mean titer in the group receiving IXIARO. There was no significant difference between seroconversion rates in subjects aged <50 years compared to those aged ≥ 50 years at Day 28 or Day 56 for either treatment group.

Antibody persistence (adults)

Antibody persistence was evaluated in an uncontrolled Phase 3 follow up clinical trial, enrolling subjects who had completed two pivotal studies, and who received at least one dose of IXIARO. Long term immunogenicity of IXIARO was assessed in a subset of 181 subjects up to month 24 (Intent-to-treat (ITT) population) and in 152 subjects up to month 36 after the first IXIARO vaccination.

Rates of subjects with $PRNT_{50} \geq 1:10$ and GMTs at Months 2, 6, 12, 24 and 36 are summarized in Table 3 for the ITT population.

Table 3: Rates of subjects with $PRNT_{50} \geq 1:10$ and geometric mean titers (GMT) at Month 2, 6, 12, 24 and 36 after vaccination with IXIARO (ITT population)

Time point	Rate of subjects with $PRNT_{50} \geq 1:10$		GMT	
	% (n/N)	95% Confidence Interval	GMT (N)	95% Confidence Interval
Month 2	98.9 (179/181)	[96.1, 99.7]	310.8 (181)	[268.8, 359.4]
Month 6	95.0 (172/181)	[90.8, 97.4]	83.5 (181)	[70.9, 98.4]
Month 12	83.4 (151/181)	[77.3, 88.1]	41.2 (181)	[34.4, 49.3]
Month 24	81.8 (148/181)	[75.5, 86.7]	44.3 (181)	[36.7, 53.4]
Month 36	84.9 (129/152)	[78.3, 89.7]	43.8 (152)	[36.5, 52.6]

The observed decline in GMT is as expected and compares well with data from other inactivated JE vaccines.

In another open-label, follow-up Phase 3 study, the persistence of antibodies up to 24 months after primary vaccination was assessed. A total of 116 subjects who had received the recommended primary schedule of IXIARO were included in this follow-up study. Rates of subjects with PRNT₅₀≥1:10 were 82.8% (95% CI: 74.9, 88.6, N=116) at Month 6 and 58.3% at Month 12 (95% CI: 49.1, 66.9, N=115). At Month 24, 48.3% (95% CI: 39.4, 57.3, N=116) of subjects who completed the recommended primary immunization still had PRNT₅₀ titers of ≥1:10. GMT in these subjects was 16.2 (95% CI: 13.8, 19.0) at Month 24.

Booster immunisation (adults)

In an uncontrolled, open-label phase 3 study a single 6 mcg (0.5 ml) booster dose of IXIARO was given at month 15 after primary immunization. All of the 198 subjects treated were included in the ITT and Safety Populations.

Rates of subjects with PRNT₅₀≥1:10 and GMT over time are summarised in table 4:

Table 4: Rates of subjects with PRNT₅₀≥1:10 and GMT before and at months 1, 6 and 12 after a single 6 mcg (0.5 ml) booster dose administered to subjects at 15 months after recommended primary immunization with IXIARO (ITT population)

	Rate of subjects with PRNT ₅₀ ≥1:10		GMT	
		95% CI		95% CI
Pre-booster, Day 0 (n=198)	69.2%	[62.4%, 75.2%]	22.5	[19.0, 26.7]
Day 28 (n=198)	100.0%	[98.1%, 100.0%]	900.1	[742.4, 1091.3]
Month 6 (n=197)	98.5%	[95.6%, 99.5%]	487.4	[390.7, 608.1]
Month 12 (n=194)	98.5%	[95.6%, 99.5%]	361.4	[294.5, 443.5]

Antibody persistence after booster immunisation (adults)

In an uncontrolled, open-label extension to the booster study described above, 67 subjects were followed up for determination of JEV neutralizing antibody titres at approximately 6 years after a booster dose. 96% of subjects (64/67) still had protective antibody levels (PRNT₅₀≥1:10), with a GMT of 148 (95% CI: 107; 207). Mathematical modelling was applied to project the average duration of protection. Based on this model, it is estimated that average duration of protection will be 14 years and 75% of vaccinees will retain protective antibody levels (PRNT₅₀≥1:10) for 10 years. A second booster should therefore be given 10 years after the first booster dose, administered 1 year after the primary immunization, prior to potential exposure to JEV.

Rapid immunisation schedule (adults)

The immunogenicity of IXIARO administered in a rapid vaccination schedule was evaluated in a randomized, observer-blind, phase 3 study. A total of 217 subjects aged 18 to ≤ 65 years received IXIARO together with inactivated rabies vaccine (Rabipur) in a rapid immunisation schedule on Day 0 and Day 7 and 56 subjects received IXIARO alone in the conventional immunisation schedule on Day 0 and Day 28. The proportion of subjects that seroconverted by 7 and by 28 days after the last immunisation was similar for both schedules. Seroconversion rates and antibody titers also remained comparably high up to 12 months after the first immunisation in both schedules (Table 5).

The rapid schedule was tested for concomitant administration of IXIARO and Rabipur but it can also be used for administration of IXIARO alone, as no immune interference of the two vaccines has been observed (see section 4.5).

Table 5: Seroconversion rates and GMTs for anti-JEV neutralizing antibodies on Day 0, 14, 21, 35, 56 and 365 after immunisation with IXIARO and inactivated rabies vaccine in a rapid schedule and IXIARO alone in a conventional schedule (Per Protocol population)

	Seroconversion Rate (Rate of subjects with PRNT ₅₀ ≥1:10)		GMT (plaque reduction neutralization test)	
	Rapid Schedule % (n/N)	Conventional Schedule % (n/N)	Rapid Schedule (N)	Conventional Schedule (N)
Vaccination scheme	IXIARO Day 0,7 Rabipur Day 0,3,7	IXIARO Day 0,28 -	IXIARO Day 0,7 Rabipur Day 0,3,7	IXIARO Day 0, 28 -
Day 0	6 (13/215)	9 (5/55)	5.63 (215)	5.73 (55)
Day 14	99 (206/209)	NA	715 (209)	NA
Day 21	100 (207/208)	NA	1255 (208)	NA
Day 35	99 (203/206)	100 (47/47)	690 (206)	376 (47)
Day 56	98 (200/204)	100 (49/49)	372 (204)	337 (49)
Day 365	94 (188/199)	88 (42/48)	117 (199)	39 (48)

NA= not applicable

Incomplete primary immunization (adults)

The immunogenicity of booster doses was also assessed in the study investigating persistence of immunity following different primary immunization regimens (2x6 mcg: N=116, 1x12mcg: N=116 or 1x6 mcg: N=117). A single 6 mcg (0.5 ml) booster dose was administered at 11 or 23 months after the first dose to subjects, which were determined to be seronegative (PRNT₅₀ titers < 1:10) at month 6 and/or month 12 after the primary immunization. Results indicate that the second injection of the primary immunization series can be given up to 11 months after the first dose. The immune responses to further doses at different time points after complete or incomplete primary immunization are shown in table 6.

Table 6: SCR and GMT at four weeks after a single 6 mcg booster dose administered to subjects with a PRNT₅₀<1:10 (PRNT₅₀<1:10 means a subject is no longer seroprotected) at month 11 or month 23 after recommended primary immunization (2x 6 mcg) or incomplete (1x6 mcg) primary immunization with IXIARO (ITT population)

	(n / N)	SCR	GMT	[95% CI]
Booster following recommended primary immunization (2x6 mcg)				
Booster at Month 11	(17 / 17)	100 %	673.6	[378.7, 1198.2]
Booster at Month 23	(27 / 27)	100 %	2536.7	[1467.7, 4384.4]
Second dose following incomplete primary immunization (1x6 mcg)				
Second dose at Month 11	(99 / 100)	99 %	504.3	[367.3, 692.3]
Second dose at Month 23	(5 / 5)	100 %	571.4	[88.2, 3702.9]

Concomitant use (adults)

Concomitant administration of IXIARO with inactivated hepatitis A virus (HAV) vaccine (HAVRIX 1440)

The concomitant use of IXIARO with inactivated hepatitis A virus (HAV) vaccine (HAVRIX 1440) has been explored in one clinical trial. There was no interference with the immune response to the JE virus and HAV, respectively. Concomitant administration of IXIARO and inactivated hepatitis A vaccine was shown to be non-inferior to single vaccinations with regard to GMT of anti-JE virus neutralizing antibody and HAV antibody, and for seroconversion rates of both antibody types (Table 7).

Table 7: Seroconversion rates and geometric mean titer of anti JEV neutralizing antibody at Day 56 and seroconversion rates and geometric mean titer for HAV antibody at Day 28 in the Per Protocol Population

Seroconversion rates and geometric mean titer for anti-JEV neutralizing antibody at Day 56			
	% with SCR	GMT	95% CI
Group C: IXIARO + HAVRIX1440	100.0	202.7	[153.7, 261.2]
Group A: IXIARO + Placebo	98.2	192.2	[147.9, 249.8]
Seroconversion rates and geometric mean titer for HAV antibody at Day 28			
	% with SCR	GMT	95% CI
Group C: IXIARO + HAVRIX 1440	100.0	150.0	[111.7, 202.3]
Group B: HAVRIX + Placebo	96.2	124.0	[91.4, 168.2]

Concomitant administration of IXIARO with inactivated rabies vaccine (Rabipur):

In an observer-blind Phase 3 study, concomitant administration of IXIARO and Rabipur has been studied in adults aged 18 to ≤ 65 years of age in comparison to respective single vaccinations in conventional schedule. No interference was observed with regards to geometric mean titer (GMT) and seroconversion rates for anti JEV neutralizing antibodies (Table 8). There was also no interference with the immune response to Rabipur.

Table 8: Seroconversion rates (rate of subjects with PRNT₅₀≥1:10) and GMTs (plaque reduction neutralization test) for anti-JEV neutralizing antibodies after administration of IXIARO and Rabipur in conventional schedule, Per Protocol population

Seroconversion rates and geometric mean titer for JEV neutralizing antibody at Day 56		
	SCR [%] (n/N)	GMT [95% CI] (N)
IXIARO + Rabipur	100 (157/157)	299 [254-352] (157)
IXIARO	100 (49/49)	337 [252-451] (49)

Vaccination schedules: IXIARO: Day 0/28, Rabipur: Day 0/7/28.

Immunogenicity in elderly persons (>65 years)

The immunogenicity of IXIARO was evaluated in an open-label, uncontrolled trial in 200 healthy elderly persons aged >65 to 83 years, including subjects with stable underlying conditions like hypercholesterolemia, hypertension, cardiovascular disease or non insulin-dependent diabetes mellitus. JEV neutralizing antibodies were determined 42 days after the second dose of the primary series (Day 70).

Elderly persons have a lower immune response to vaccination compared to younger adults or children, in terms of seroconversion rates (percentage of subjects with PRNT₅₀ titer ≥1:10) and geometric mean titers (Table 9).

Table 9: Seroconversion rates and geometric mean titer of JEV neutralizing antibody at Day 70 in the Intent-to-treat Population, for the entire study population and stratified by age

Seroconversion rates and geometric mean titer for JEV neutralizing antibody at Day 70				
	n / N	SCR	GMT	95% CI
Total Study Population	128/197	65%	37	29.2, 47.8
Age group >65 - <75years	113/173	65.3%	37.2	28.6, 48.3
Age group ≥75 years	15/23	65.2%	42.2	19.2, 92.7

Paediatric population

In a phase 2 study in healthy Indian toddlers aged ≥ 1 year to < 3 years, 24 children were vaccinated with 0.25 ml of IXIARO (the licensed dose for this age group) and 24 children received the adult 0.5 ml dose. Data are limited but there were no differences in the safety profile between the 0.25 ml and the 0.5 ml dose in this age group.

Immunogenicity and safety of IXIARO in children and adolescents from a JEV-endemic country

The safety and immunogenicity of IXIARO were evaluated in a randomized, controlled, open-label clinical trial conducted in the Philippines, where JEV is endemic. The safety profile of IXIARO was compared to control vaccines Havrix (Hepatitis A vaccine, paediatric 720 EL.U./0.5 mL formulation) and Prevenar (Pneumococcal 7-valent Conjugate Vaccine [Diphtheria CRM197 protein]). The immunogenicity evaluation was performed in a subset of the study population and included the determination of the seroconversion rate (SCR), defined as JEV neutralizing antibody titer $\geq 1:10$, the proportion of subjects achieving an at least four-fold increase in antibody titers and the geometric mean titer (GMT) at Day 56 and Month 7, by dose and by age group. The immune responses elicited by IXIARO are presented in Table 10.

Table 10: Seroconversion rates, rates of subjects with at least 4-fold increase in JEV neutralizing antibody titers and Geometric Mean Titers at baseline, Day 56 and Month 7 stratified by age group, Intent To Treat Population

Vaccine Dose	0.25 ml			0.5 ml	
Age Group	2 months – <6 months	6 months – <12 months	1 year – < 3 years	3 years - < 12 years	12 years - < 18 years
Seroconversion Rates % (n/N)					
Pre-Vaccination	30% (3/10)	0% (0/20)	3.2% (4/125)	16.8% (17/101)	45.7% (64/140)
Day 56	100% (9/9)	100% (19/19)	99.2% (119/120)	100.0% (100/100)	100% (137/137)
Month 7	100% (10/10)	100% (18/18)	85.5% (106/124)	91.0% (91/100)	97.1% (133/137)
Proportion of Subjects Achieving an \geq4-fold Increase in JEV Antibody Titers % (n/N)					
Day 56	100 (9/9)	94.7 (18/19)	96.7 (116/120)	94.0 (94/100)	77.4 (106/137)
Month 7	90.0 (9/10)	83.3 (15/18)	75.8 (94/124)	71.0 (71/100)	65.0 (89/137)
Geometric Mean Titer (N)					
Pre-Vaccination	8.42 (10)	5 \diamond (20)	5.52 (124)	6.54 (101)	13.08 (140)
Day 56	687.35 (9)	377.79 (19)	258.90 (121)	213.67 (100)	175.63 (137)
Month 7	159.27 (10)	64.00 (18)	38.91 (125)	43.60 (100)	86.61 (137)

\diamond Negative Pre-Vaccination titers were imputed to 5.

Safety and tolerability was evaluated in the entire study population. Parents or subjects recorded adverse events on a diary card for the first seven days after each vaccination. Parents or subjects were asked for any unsolicited AEs on the day of the second vaccination and at in-person visits including a medical exam 28 days (Day 56) and 6 months (Month 7) after the second dose. The safety profile of IXIARO was comparable to that of Havrix or Prevenar.

Antibody persistence and booster dose in children and adolescents from a JEV-endemic country

The persistence of JEV neutralizing antibodies after primary immunisation and safety and immunogenicity of an IXIARO booster dose 12 months after primary immunization were evaluated in a randomized, controlled, open-label clinical trial conducted in the Philippines, where JEV is endemic (300 children, mean age 5.3 years, range 1.2 - 17.3 years). 150 children were followed-up for three years without booster, additional 150 children received a booster after 1 year (0.25 ml if aged <3 years at time of the booster, 0.5 ml if aged 3 years and above) and were followed-up for further two years. Seroprotection rate (SPR) defined as neutralizing antibody titer \geq 1:10 and geometric mean titers (GMT) are presented in Table 11. The booster dose led to a pronounced increase in GMTs and seroprotection rate remained at 100% two years after the booster.

Table 11: Seroprotection Rates and Geometric Mean Titers with and without a booster of IXIARO at Month 12, 13, 24 and 36, Intent To Treat Population

	Without Booster N = 150	Booster dose 12 months after primary immunization N = 149	
Time point after primary immunization		0.25 mL Booster Dose N=81	0.5 mL Booster Dose N=67
Seroprotection Rate % (n/N)			
Month 12	89.9 (134/149)	97.5 (79/81)	89.6 (60/67)
Month 13	n.a.	100 (81/81)	100.0 (67/67)
Month 24	89.0 (130/146)	100 (80/80)	100.0 (67/67)
Month 36	90.1 (128/142)	100.0 (76/76)	100.0 (67/67)
Geometric Mean Titer			
Month 12	46	67	40
Month 13	n.a.	2911	1366
Month 24	50	572	302
Month 36	59	427	280

n.a. = not available

Immunogenicity and safety in children and adolescents from non-endemic countries

The safety and immunogenicity of IXIARO was evaluated in an uncontrolled, open-label clinical trial conducted in the United States, Europe and Australia in healthy male and female subjects with planned travel to JEV-endemic areas. Children and adolescents aged ≥ 3 to < 18 years received two vaccine doses of 0.5ml and children aged ≥ 2 months to < 3 years received two vaccine doses of 0.25ml on Day 0 and Day 28 by intramuscular injection. Immunogenicity data were evaluated in 64 subjects. The SCRs and GMTs are displayed in Table 12.

Table 12: Seroconversion rates and geometric mean titer of JEV neutralizing antibody by vaccine dose and age group. Intent-to-treat Population

	IXIARO Dose	Time Point	SCR n / N	GMT	95% CI
Age Group ≥ 2 months to < 3 years	0.25 ml	Day 56	100% 5/5	216.2	106.0; 441.0
		Month 7	100% 2/2	48.0	0.0; 3214485.7
Age Group ≥ 3 to < 18 years	0.5 ml	Day 56	100% 57/57	340.7	269.8; 430.3
		Month 7	90.6% 29/32	57.1	38.4; 84.9

Antibody persistence in children and adolescents from non-endemic countries

Antibody persistence was evaluated for three years after the primary vaccination with IXIARO in an uncontrolled, open-label follow-up clinical trial conducted in the United States, Europe and Australia. Long-term immunogenicity data were evaluated in 23 children, mean age 14.3 years, range 3 - 18 years). The SPRs and GMTs are displayed in Table 13.

Table 13: Seroprotection rates and geometric mean titer of JEV neutralizing antibody by vaccine dose and age group. Intent-to-treat Population

	Seroprotection Rate (Rate of subjects with PRNT ₅₀ ≥1:10) % (n/N)		Geometric Mean Titer (plaque reduction neutralization test) GMT [95% CI]	
	After 0.25 mL Dose Primary Immunization	After 0.5 mL Dose Primary Immunization	After 0.25 mL Dose Primary Immunization	After 0.5 mL Dose Primary Immunization
Month 12	0% (0/0)	89.5% (17/19)	-	48 [28; 80]
Month 24	100% (1/1)	90.9% (20/22)	193 [n.a.]	75 [46; 124]
Month 36	100% (1/1)	88.9% (16/18)	136 [n.a.]	61 [35; 106]

n.a. 95% Confidence Interval could not be established (single-subject data)

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical toxicity data are limited.

In a reproductive and pre-/post-natal toxicity study, no vaccine-related effects were detected on reproduction, foetal weight, survival and development of the off-spring. However, incomplete ossification of parts of the skeleton was observed in the group receiving 2 doses, but not in the group receiving 3 doses. It is currently difficult to explain if this phenomenon is treatment related or not.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Phosphate buffered saline consisting of:

Sodium chloride
Potassium dihydrogen phosphate
Disodium hydrogen phosphate
Water for injections

For adjuvant, see section 2.

6.2 Incompatibilities

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

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Store in the original package in order to protect from light.

6.5 Nature and contents of container

0.5 ml of suspension in a pre-filled syringe (Type I glass) with a plunger stopper (chlorobutyl elastomer).

Pack size of 1 syringe with or without a separate needle.

6.6 Special precautions for disposal and other handling

The pre-filled syringe is for single use only and should not be used for more than one person. The pre-filled syringe is ready to use. If a needle is not provided, use a sterile needle.

Do not use if the blister foil is not intact or packaging is damaged.

Upon storage, a fine white deposit with a clear colourless supernatant can be observed.

Before administration, shake the syringe well to obtain a white, opaque, homogeneous suspension. Do not administer if particulate matter remains following shaking or if discoloration is observed or if the syringe appears to be physically damaged..

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Information on the administration of a 0.5 ml dose of IXIARO for persons 3 years of age and above

For administration of the full 0.5 ml dose follow the steps below:

1. Shake the syringe to obtain a homogeneous suspension.
2. Remove the syringe tip cap by gently twisting it. Do not attempt to snap or pull the tip off as this may damage the syringe.
3. Attach a needle to the pre-filled syringe.

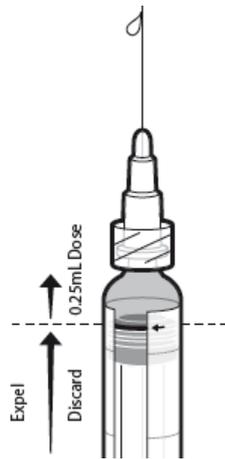
Information on the preparation of a 0.25 ml dose of IXIARO for use in children below 3 years of age

For administration of a 0.25 ml dose in children aged 2 months to < 3 years, follow the steps below:

1. Shake the syringe to obtain a homogeneous suspension.
2. Remove the syringe tip cap by gently twisting it. Do not attempt to snap or pull the tip off as this may damage the syringe.
3. Attach a needle to the pre-filled syringe.
4. Hold the syringe in an upright position.
5. Push the plunger stopper up to the edge of the red line on the syringe barrel, indicated by a red arrow (see Figure 1)*, to discard excess volume.
6. Attach a new sterile needle prior to injection of the remaining volume.

* If you pushed the plunger stopper beyond the red line, a 0.25 ml dose is not guaranteed and a new syringe should be used.

**Figure 1:
Preparation for
Administration of
0.25 ml Dose**



7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/501/001
EU/1/08/501/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 March 2009
Date of latest renewal: 22 November 2018

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>