ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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 SA_{14}-14-2 (inactivated)[1,2] 6 AU[3]
corresponding to a potency of ≤ 460 ng ED50

[1] produced in Vero cells
[2] adsorbed on aluminium hydroxide, hydrated (approximately 0.25 milligrams Al^{3+})
[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 ≤ 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 ≤ 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: ≥ 1/10
Common: ≥ 1/100 to < 1/10
Uncommon: ≥1/1,000 to < 1/100
Rare: ≥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)

	Frequency of adverse reactions(%) by dose/age	
System Organ Class Preferred Term	**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 ≥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 SA_{14}-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 $PRNT_{50}$≥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 $PRNT_{50}$≥1:10 and geometric mean titers (GMT) at Month 2, 6, 12, 24 and 36 after vaccination with IXIARO (ITT population)

	Rate of subjects with $PRNT_{50}$≥1:10		GMT	
Time point	% (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 $PRNT_{50} \geq 1:10$ 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 $PRNT_{50}$ 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 $PRNT_{50} \geq 1:10$ and GMT over time are summarised in table 4:

Table 4: Rates of subjects with $PRNT_{50} \geq 1:10$ 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 $PRNT_{50} \geq 1:10$		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 ($PRNT_{50} \geq 1:10$), 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 ($PRNT_{50} \geq 1:10$) 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 $PRNT_{50} \geq 1:10$)		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 ($PRNT_{50}$ 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 $PRNT_{50}$ <1:10 ($PRNT_{50}$<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 $\leq$ 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 $PRNT_{50} \geq 1:10$) 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 $PRNT_{50}$ titer $\geq 1:10$) 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 ≥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 ≥4-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 ◊ (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)

◊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 ≥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 $PRNT_{50} \geq 1:10$) % (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

2 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.

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

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.

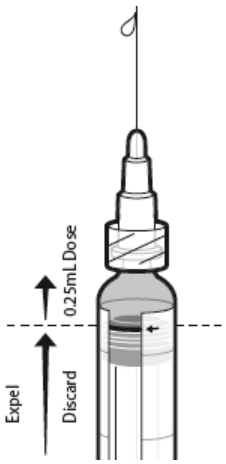
<u>Information on the preparation of a 0.25 ml dose of IXIARO for use in children below 3 years of age</u>

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

Valneva Austria GmbH
Campus Vienna Biocenter 3
A-1030 Vienna
Austria

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

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Valneva Scotland Ltd.
Oakbank Park Road
Livingston EH53 0TG
United Kingdom

Name and address of the manufacturer(s) responsible for batch release

Valneva Scotland Ltd.
Oakbank Park Road
Livingston EH53 0TG
United Kingdom

Valneva Austria GmbH
Campus Vienna Biocenter 3
1030 Wien
Austria

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 Directive 2001/83/EC as amended, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS OR REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

IXIARO suspension for injection
Japanese encephalitis vaccine (inactivated, adsorbed)
Presentation for adults, adolescents and children

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml) of IXIARO contains:
6 AU (Antigen Units, corresponding to a potency of ≤ 460 ng ED_{50}) of inactivated Japanese encephalitis virus strain SA_{14}-14-2 (produced in Vero cells) adsorbed on aluminium hydroxide, hydrated (approximately 0.25 milligrams Al^{3+}).

3. LIST OF EXCIPIENTS

Excipients:
Phosphate buffered solution consisting of sodium chloride, potassium dihydrogen phosphate, disodium hydrogen phosphate and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.
0.5 ml single dose in a pre-filled syringe.
0.5 ml single dose in a pre-filled syringe + 1 needle.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular (IM) use.
Shake to form a uniform suspension.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not inject intravascularly.

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Valneva Austria GmbH
Campus Vienna Biocenter 3
A-1030 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

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

13. BATCH NUMBER AND PRODUCT CODES

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister foil

Blank white foil without any printed information.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pre-filled syringe label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

IXIARO suspension for injection
Japanese encephalitis vaccine
Intramuscular (IM) use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose, 0.5 ml

6. OTHER

Store in a refrigerator
Do not freeze.

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

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

Read all of this leaflet carefully before you or your child receive this vaccine because it contains important information for you.

- Keep this leaflet. You and your child may need to read it again.
- If you have any further questions, ask your doctor.
- This vaccine has been prescribed for you and/or your child only. Do not pass it on to others.
- If you and/or your child get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What IXIARO is and what it is used for

IXIARO is a vaccine against the Japanese encephalitis virus.
The vaccine causes the body to produce its own protection (antibodies) against this disease.

IXIARO is used to prevent infection with the Japanese encephalitis virus (JEV). This virus is mainly found in Asia and is transmitted to humans by mosquitoes that have bitten an infected animal (like pigs). Many infected people develop mild symptoms or no symptoms at all. In people who develop severe disease, JE usually starts as a flu-like illness, with fever, chills, tiredness, headache, nausea, and vomiting. Confusion and agitation also occur in the early stage of disease.

IXIARO should be given only to adults, adolescents, children and infants aged 2 months and older travelling to countries, where JE is endemic or who are at risk through work.

2. What you need to know before you and/or your child receive IXIARO

Do not use IXIARO:
- If you and/or your child are allergic (hypersensitive) to the active substance or any of the other ingredients of this medicine (listed in section 6).
- If you and/or your child have developed an allergic reaction after receiving a former dose of IXIARO. Signs of an allergic reaction may include an itchy rash, shortness of breath and swelling of the face and tongue.
- If you and/or your child are ill with a high fever. In this case, your doctor will postpone the vaccination.

Warnings and precautions
IXIARO must not be injected into a blood vessel.
Primary immunization should be completed at least one week prior to potential exposure to JEV.

Tell your doctor:
- If you and/or your child have experienced any health problems after previous administration of any vaccine.
- If you and/or your child have any other known allergies.
- If you and/or your child have a bleeding disorder (a disease that makes you bleed more than normal) or a reduction in blood platelets, which increases risk of bleeding or bruising (thrombocytopenia).
- If your child is younger than 2 months of age, since IXIARO has not been tested in infants younger than 2 months of age.
- If your or your child's immune system does not work properly (immunodeficiency) or you and/or your child are taking medicines affecting your immune system (such as a medicine called cortisone or cancer medicine).

Your doctor will discuss with you the possible risks and benefits of receiving IXIARO.

Please note that:
- IXIARO cannot cause the disease it protects against.
- IXIARO will not prevent infections caused by other viruses than the Japanese encephalitis virus.
- As with any other vaccine, vaccination with IXIARO may not result in protection in all cases.
- You should take appropriate precautions for you and your child to reduce mosquito bites (adequate clothing, use of repellents, mosquito nets) even after receiving IXIARO.

Other medicines and IXIARO
Studies in humans to evaluate the effectiveness and safety of medicines (clinical trials) have shown that IXIARO can be given at the same time with hepatitis A vaccine and rabies vaccine.
Tell your doctor if you and/or your child are taking or have recently taken, or might take any other medicines, including medicines obtained without a prescription or have recently received any other vaccine.

Pregnancy and breast-feeding and fertility
There are limited amount of data from the use of IXIARO in pregnant or breast-feeding women.
As a precautionary measure, the use of IXIARO during pregnancy or breast-feeding should be avoided.
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before receiving this vaccine.

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

IXIARO contains potassium and sodium
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.

3. How to use IXIARO

The recommended dosage for adults, adolescents and children aged 3 years of age and older is a total of 2 injections of 0.5 ml each:

- The first injection on Day 0
- The second injection 28 days after the first injection (Day 28).

Adults aged 18 to $\leq$ 65 years can also be vaccinated as follows:
- The first injection on Day 0
- The second injection 7 days after the first injection (Day 7).

Babies and children aged 2 months to < 3 years of age

The recommended dosage for babies and children aged 2 months to < 3 years is a total of 2 injections of 0.25 ml each:

- The first injection on Day 0
- The second injection 28 days after the first injection (Day 28).

For instruction on the preparation of the 0.25 ml dose, please refer to the end of this package leaflet.

Make sure you and/or your child finish the complete vaccination course of 2 injections. The second injection should be given at least 1 week before you and/or your child will be at risk of exposure to JE virus. If not, you and/or your child may not be fully protected against the disease.

For adults, adolescents, children and infants aged 1 year and older a booster dose can be given within the second year (i.e. 12 - 24 months) after the first dose of the recommended primary immunization. In adults, a second booster can be given 10 years after the first booster. For elderly persons (>65 years) the first booster dose may be given earlier. Your doctor will decide on the requirement and timing for booster doses.

Administration
IXIARO is injected into your or your child's upper arm muscle (deltoid muscle) by your doctor or a nurse. It must not be injected into a blood vessel. In case you and/or your child suffer from a bleeding disorder, your doctor may decide to administer the vaccine under the skin (subcutaneously).
If you have any further questions on the use of this product, ask your doctor or pharmacist.

If you forget to get IXIARO
If you and/or your child miss a scheduled injection, talk to your doctor and arrange another visit for the second injection.
Without the second injection you and/or your child will not be fully protected against the disease. There is data showing that the second injection can be given up to 11 months after the first one.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The majority of the side effects listed below have been observed during clinical trials. They usually occur within the first 3 days after vaccination, are usually mild and disappear within a few days.

Very common (affects more than 1 user in 10):
headache, muscle pain, injection site pain, injection site tenderness, tiredness

Common (affects 1 to 10 users in 100):
Nausea, influenza like illness, fever, other injection site reactions (e.g. redness, hardening, swelling, itching)

Uncommon (affects 1 to 10 users in 1,000):
vomiting, skin rash, changes in the lymph-nodes, migraine (throbbing headache, often accompanied by nausea and vomiting and sensitivity to light), dizziness, vertigo (spinning sensation), diarrhoea, belly pain, excessive sweating, itching, chills, general condition of feeling unwell, musculoskeletal stiffness, joint pain, weakness, abnormal laboratory liver test results (hepatic enzymes increased)

Rare (affects 1 to 10 users in 10,000):
palpitations, rapid heartbeat, difficulty to breathe, abnormal sensation of skin (for example pins and needles), hives, skin redness, pain in leg or arm, platelet deficiency, nerve inflammation, limb swelling and ankle swelling, taste disturbance, swelling of eyelid, fainting

Additional side effects in children aged 2 months to <3 years

In children aged 2 months to <3 years, the following side effects have been observed more frequently compared to children aged 3 years to <12 years, adolescents and adults:
Very common: fever (28.9%), diarrhoea (11.8%), influenza like illness (11.2%), irritability (11.0%)
Common: loss of appetite, vomiting, skin rash
Uncommon: cough

Reporting of side effects
If you and/or your child get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V.
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store IXIARO

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and label after "EXP". The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C - 8°C).
- Do not freeze. If the vaccine has been frozen it should not be used.
- Store in the original package in order to protect from light.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you and/or your child no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What IXIARO contains

1 dose (0.5 ml) of IXIARO contains:
Japanese encephalitis virus strain SA_{14}-14-2 (inactivated)[1,2] 6 AU[3]
corresponding to a potency of ≤ 460 ng ED_{50}

[1] produced in Vero cells
[2] adsorbed on aluminium hydroxide, hydrated (approximately 0.25 milligrams Al^{3+})
[3] Antigen Units

Aluminium hydroxide is included in this vaccine as an adjuvant.

The other ingredients are: Sodium chloride, potassium dihydrogen phosphate, disodium hydrogen phosphate, water for injections

What IXIARO looks like and contents of the pack

IXIARO is a suspension for injection (0.5 ml in a glass syringe with or without a separate needle, pack size of 1).

IXIARO is a white and slightly milky sterile suspension, which becomes homogenous on shaking.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Valneva Austria GmbH
Campus Vienna Biocenter 3

A-1030 Vienna
Austria
Email: infoixiaro@valneva.com

Manufacturer:
Valneva Scotland Ltd.
Oakbank Park Road,
Livingston EH53 0TG, Scotland,
United Kingdom

Valneva Austria GmbH
Campus Vienna Biocenter 3
A-1030 Vienna
Austria

For any information about this medicine, please contact the Marketing Authorization Holder by the following email-address:
infoixiaro@valneva.com

This leaflet was last revised in .

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.
This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

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