HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use IXIARO safely and effectively. See full prescribing information for IXIARO.

IXIARO (Japanese Encephalitis Vaccine, Inactivated, Adsorbed)
Suspension for Intramuscular Injection
Initial U.S. Approval: 2009

---------- RECENT MAJOR CHANGES ----------

Dosage and Administration, Dosage and Schedule (2.1)	10/2018
Warnings and Precautions, Syncope (5.2)	04/2018

---------- INDICATIONS AND USAGE ----------

IXIARO is a vaccine indicated for active immunization for the prevention of disease caused by Japanese encephalitis virus (JEV). IXIARO is approved for use in individuals 2 months of age and older. (1)

---------- DOSAGE AND ADMINISTRATION ----------

For intramuscular administration only.

Age	Dose*	Primary Series
Children 2 months to <3 years of age	0.25 mL	2 doses, 28 days apart
Children and adolescents 3 to <18 years of age	0.5 mL	2 doses, 28 days apart
Adults 18 through 65 years of age	0.5mL	2 doses, 7 days apart or 2 doses, 28 days apart
Adults older than 65 years of age	0.5mL	2 doses, 28 days apart

*To administer a 0.25 mL dose, expel and discard half of the volume from the 0.5 mL pre-filled syringe by pushing the plunger stopper up to the edge of the red line on the syringe barrel prior to injection. (2.3)

Complete the primary immunization series at least 1 week prior to potential exposure to JEV. (2.1, 14)

A booster dose (third dose) may be given at least 11 months after completion of the primary immunization series if ongoing exposure or re-exposure to JEV is expected.
(2.1, 14)

--------- DOSAGE FORMS AND STRENGTHS----------

Suspension for injection supplied in 0.5 mL single dose syringes.

---------- CONTRAINDICATIONS ----------

Severe allergic reaction, (e.g., anaphylaxis,) after a previous dose of IXIARO, any other Japanese Encephalitis Virus vaccine, or any component of IXIARO, including protamine sulfate, is a contraindication to administration of IXIARO. (4)

---------- WARNINGS AND PRECAUTIONS----------

IXIARO contains protamine sulfate, a compound known to cause hypersensitivity reactions in some individuals. (5.1)

---------- ADVERSE REACTIONS ----------

In infants 2 months to <1 year of age, the most common injection site reaction was redness (>15%); the most common solicited systemic adverse reactions were fever (>20%), irritability (>15%) and diarrhea (>10%). (6.1)

In children 1 to <3 years of age, the most common solicited systemic adverse reaction was fever (>20%). (6.1)

In children 3 to <12 years of age, the most common solicited systemic adverse reaction was fever (>10%). (6.1)

In adolescents 12 to <18 years of age, the most common injection site reactions were pain (15%) and tenderness (10%). (6.1)

In adults 18 years of age and older, the most common injection site reactions were pain (>25%) and tenderness (>25%); the most common solicited systemic adverse reactions were headache (>20%) and myalgia (>10%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Valneva USA, Inc. at 844-349-4276 (8443-IXIARO) or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

---------- USE IN SPECIFIC POPULATIONS ----------

To report use in pregnant women, contact Valneva USA, Inc. at 844-349-4276 (8443-IXIARO).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling (Patient Information).

Revised 10/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

IXIARO is a vaccine indicated for the prevention of disease caused by Japanese encephalitis virus (JEV). IXIARO is approved for use in individuals 2 months of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular administration only.

2.1 Dosage and Schedule

Primary Series:

Children 2 months to <3 years of age: Primary immunization with IXIARO consists of two (2) 0.25 mL doses, administered 28 days apart.

Children and adolescents 3 to <18 years of age: Primary immunization with IXIARO consists of two (2) 0.5 mL doses, administered 28 days apart.

Adults18 through 65 years of age: Primary immunization with IXIARO consists of two (2) 0.5 mL doses, administered 7 days apart, or two (2) 0.5 mL doses, administered 28 days apart.

Adults older than 65 years of age: Primary immunization with IXIARO consists of two (2) 0.5 mL doses, administered 28 days apart.

Complete the primary immunization series at least 1 week prior to potential exposure to JEV.

Booster Dose:

A booster dose (third dose) may be given at least 11 months after completion of the primary immunization series if ongoing exposure or re-exposure to JEV is expected.

Children from 14 months to < 3 years of age should receive a single 0.25 mL booster dose. Individuals 3 years of age and older should receive a single 0.5 mL booster dose.

2.2 Administration

IXIARO is administered intramuscularly. The preferred sites for intramuscular injection are the anterolateral aspect of the thigh in infants 2 to 11 months of age, the anterolateral aspect of the thigh (or the deltoid muscle if muscle mass is adequate) in children 1 to <3 years of age, or the deltoid muscle in individuals 3 years of age and older.

Do not administer intravenously, intradermally, or subcutaneously.

2.3 Preparation for Administration

Prior to agitation, IXIARO is a clear liquid with a white precipitate. Before administration, shake the syringe well to obtain a white, opaque, homogeneous suspension.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. If either of these conditions exists, do not administer.

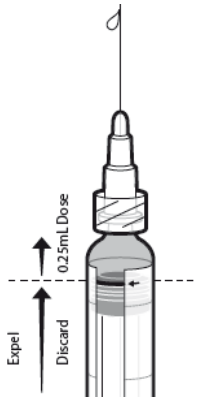
<u>Preparation of a 0.25 mL Dose of IXIARO for Administration to Children 2 Months to <3 Years of Age:</u>

1. Shake the pre-filled syringe containing 0.5 mL 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 sterile safety needle to the pre-filled syringe (needle is not provided with IXIARO).
4. Hold the syringe in an upright position and uncap the needle.
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)*, and discard expelled volume into a medical waste container.
6. Lock the needle safety shield and remove the needle.
7. Attach a new sterile needle prior to injection of the remaining volume.

*If the plunger stopper is pushed beyond the red line, do not administer the vaccine. Repeat the procedure using a new pre-filled syringe.

Figure 1: Preparation for Administration of 0.25 mL Dose



Preparation of a 0.5 mL Dose of IXIARO for Administration to Individuals 3 Years of Age and above:

1. Shake the pre-filled syringe containing 0.5 mL 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 sterile needle to the pre-filled syringe (needle is not provided with IXIARO).

3 DOSAGE FORMS AND STRENGTHS

IXIARO is a suspension for injection supplied in 0.5 mL single dose syringes. For children 2 months to <3 years of age, a single dose is 0.25 mL. For individuals 3 years of age and older, a single dose is 0.5 mL. [*See Dosage and Administration (2.1)*]

4 CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of IXIARO, any other Japanese Encephalitis Virus vaccine, or any component of IXIARO, including protamine sulfate, is a contraindication to administration of IXIARO [*See Description (11)*]. Alternatively, because of uncertainty as to which component of the vaccine may be responsible, individuals with a history of severe allergic reaction to another Japanese Encephalitis vaccine may be referred to an allergist for evaluation if immunization with IXIARO is considered.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

IXIARO contains protamine sulfate, a compound known to cause hypersensitivity reactions in some individuals [*See Description (11)*]. Appropriate medical care should be readily available in case of anaphylactic reaction.

5.2 Syncope

Syncope (fainting) can occur in association with administration of injectable vaccines including IXIARO. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope.

5.3 Limitations of Vaccine Effectiveness

Vaccination with IXIARO may not protect all individuals.

5.4 Altered Immunocompetence

Immunocompromised individuals may have a diminished immune response to IXIARO.

6 ADVERSE REACTIONS

In infants 2 months to <1 year of age, the most common injection site reaction was redness (>15%); the most common solicited systemic adverse reactions were fever (>20%), irritability (>15%) and diarrhea (>10%). In children 1 to <3 years of age, the most common solicited systemic adverse reaction was fever (>20%). In children 3 to <12 years of age, the most common solicited systemic adverse reaction was fever (>10%). In adolescents 12 to <18 years of age, the most common solicited injection site reactions were pain (15%) and tenderness (10%).

In adults 18 years of age and older, the most common injection site reactions were pain (>25%) and tenderness (>25%); the most common solicited systemic adverse reactions were headache (>20%) and myalgia (>10%).

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

Clinical Studies in Children and Adolescents 2 Months to <18 Years of Age:

Adverse Events in a Pediatric Trial of IXIARO Days 0 and 28 Primary Series in a JEV-Endemic Country:

The safety of the IXIARO Days 0 and 28 primary series was evaluated in a randomized, controlled, open-label clinical trial in healthy male and female subjects 2 months to <18 years of age, conducted in the Philippines, a country where Japanese Encephalitis is endemic (Study 1)[1]. IXIARO was compared to two control vaccines: HAVRIX (Hepatitis A vaccine, pediatric 720 EL.U./0.5 mL formulation, GlaxoSmithKline Biologicals) and Prevnar (Pneumococcal 7-valent Conjugate Vaccine [Diphtheria CRM197 protein], Pfizer). A total of 1,769 subjects were randomized in an age-stratified scheme in a 3:1 ratio (2:1 ratio for ages <1 year) to receive intramuscular injections of either IXIARO (two 0.25 mL doses on Days 0 and 28 for infants and children 2 months to <3 years of age or two 0.5 mL doses on Days 0 and 28 for children 3 to <18 years of age) or HAVRIX (children 1 year of age and older, 2 doses on Day 0 and at Month 7) or Prevnar (infants 2 to <6 months of age, 3 doses on Days 0, 28, 56 and an optional 4th dose at Month 7 or later; infants 6 to <12 months of age, 3 doses on Days 0 and 56 and at Month 7).

Analysis of safety for the primary series in children was carried out using the safety population including 1,311 subjects receiving at least one dose of IXIARO, 394 subjects receiving the first

dose of HAVRIX on Day 0, and 64 subjects receiving at least one dose of Prevnar on Day 0 (all infants <1 year of age). The IXIARO and control groups were similar with regard to demographics (mean age 5.48 years, range 2 months to 17 years; 49.5% female; ethnicity: Asian: 100% for Study 1[1] overall). In both studies, parents or subjects recorded adverse reactions on a diary card for the first seven days after each vaccination. Only those events considered to be assessable based on the subject's developmental status were recorded. Parents or subjects were queried regarding the occurrence of any unsolicited adverse events following the previous vaccination at in-person visits, which included a medical exam, on Day 28, Day 56, and at Month 7 after the primary series.

For an overview of solicited local and systemic reactions following IXIARO Days 0 and 28 primary series vaccinations see Table 1 (infants 2 months to <1 year of age), Table 2 (toddlers 1 to <3 years of age) Table 3 (children 3 to <12 years of age), and Table 4 (adolescents 12 to <18 years of age). As children 1 year of age and older received the second dose of HAVRIX at the final study visit at Month 7, rates of solicited adverse reactions among these subjects after the second vaccination are only available for IXIARO.

Table 1. Rates of Solicited Adverse Reactions on Days 0-7 After Each Vaccination in Infants 2 Months to <1 Year of Age, by Dose and Treatment Group, Study 1[§], Philippines

	Post Dose 1 (% of subjects)		**Post Dose 2 (% of subjects)**	
Injection Site Reactions	**IXIARO* (N=131‡)**	**Prevnar (N=64‡)**	**IXIARO* (N=131‡)**	**Prevnar (N=64‡)**
Tenderness	3.1	12.7	0.8	3.3
Hardening	0.0	7.9	0.0	1.6
Swelling	1.5	6.3	1.5	1.6
Redness	17.6	25.4	5.3	16.4
Solicited Systemic Reactions				
Irritability	15.3	12.7	8.4	8.2
Vomiting	7.6	6.3	3.8	1.6
Diarrhea	11.5	6.3	8.4	4.9
Excessive fatigue	3.1	7.9	1.5	3.3
Rash	8.4	9.5	3.8	4.9
Loss of appetite	5.3	9.5	5.3	6.6
Fever ≥37.7°C (≥99.9°F)	23.7	25.4	14.5	23.3
37.7-38.6°C (99.9-101.5°F)	17.6	22.2	12.2	15.0
38.7-39.3°C (101.6-102.7°F)	6.1	1.6	1.5	6.7
39.4-40.5°C (102.8-104.9°F)	0.0	1.6	0.8	1.7
>40.5°C (>104.9°F)	0.0	0.0	0.0	0.0

[§]NCT01041573

* IXIARO dose 0.25 mL on Days 0 and 28.

‡N=number of subjects with available diary card data after each dose, used as the denominator to calculate percentages.

Table 2. Rates of Solicited Adverse Reactions on Days 0-7 After Each Vaccination in Children 1 Year to <3 Years of Age, by Dose and Treatment Group, Study 1[§], Philippines

	Post Dose 1 (% of subjects)**		**Post Dose 2 (% of subjects**)**
Injection Site Reactions	**IXIARO* (N=640‡)**	**Havrix (N=213‡)**	**IXIARO* (N=637‡)**
Pain	3.6 (6/165)	7.4 (4/54)	3.6 (6/166)
Itching	0.6 (1/180)	0.0 (0/63)	0.0 (0/184)
Tenderness	3.1	5.6	1.4
Hardening	0.9	0.5	0.3
Swelling	2.0	3.3	1.7
Redness	6.1	7.5	2.5
Solicited Systemic Reactions			
Irritability	7.7	5.6	2.7
Nausea	2.2 (5/228)	1.3 (1/78)	0.9 (2/229)
Vomiting	4.2	5.6	2.8
Diarrhea	7.0	5.2	4.6
Flu-like symptoms	7.7 (13/169)	13.3 (8/60)	4.0 (7/176)
Excessive fatigue	2.5	0.9	1.1
Muscle pain	2.3 (3/130)	0.0 (0/42)	0.7 (1/136)
Rash	4.2	2.3	1.3
Headache	1.5 (2/135)	4.4 (2/45)	1.4 (2/143)
Loss of appetite	5.6	4.2	2.5
Fever ≥37.7°C (≥99.9°F)	20.2	15.5	12.7
37.7-38.6°C (99.9-101.5°F)	15.6	12.2	8.5
38.7-39.3°C (101.6-102.7°F)	3.0	1.4	2.5
39.4-40.5°C (102.8-104.9°F)	1.6	1.9	1.6
>40.5°C (>104.9°F)	0.0	0.0	0.2

[§]NCT01041573

*IXIAROdose 0.25 mL on Days 0 and 28.

‡N=number of subjects with available diary card data after each dose, used as the denominator to calculate percentages

**Where the number of subjects with available data for a particular symptom differed from the overall number of subjects with available diary card data, the rate (n/N) is provided; n is the number of subjects who reported that symptom, and N is the number of subjects with available data for that symptom.

Table 3. Rates of Solicited Adverse Reactions on Days 0-7 After Each Vaccination in Children 3 Years to <12 Years of Age, by Dose and Treatment Group, Study 1[§], Philippines

	Post Dose 1 (% of subjects)		**Post Dose 2 (% of subjects)**
Injection Site Reactions	**IXIARO* (N=291-300‡)**	**Havrix (N=99-101‡)**	**IXIARO* (N=293-300‡)**
Pain	5.5	3.0	1.7
Itching	1.4	0.0	0.0
Tenderness	4.3	1.0	2.0
Hardening	1.3	0.0	0.0
Swelling	2.0	3.0	2.0
Redness	3.0	1.0	0.7
Solicited Systemic Reactions			
Irritability	0.0	1.0	0.3
Nausea	0.3	0.0	0.3
Vomiting	1.7	1.0	0.7
Diarrhea	0.7	0.0	1.0
Flu-like symptoms	1.4	2.0	0.3
Excessive fatigue	1.0	1.0	0.7
Muscle pain	2.4	3.0	0.3
Rash	1.0	0.0	0.0
Headache	3.8	4.0	1.4
Loss of appetite	1.0	2.0	1.0
Fever ≥37.7°C (≥99.9°F)	10.7	8.9	4.7
37.7-38.6°C (99.9-101.5°F)	7.7	6.9	3.3
38.7-39.3°C (101.6-102.7°F)	2.0	2.0	0.7
39.4-40.5°C (102.8-104.9°F)	1.0	0.0	0.7
>40.5°C (>104.9°F)	0.0	0.0	0.0

[§]NCT01041573

*IXIARO dose 0.5 mL on Days 0 and 28.

‡N=range of subjects with available diary card data after each dose, used as denominators to calculate percentages.

Table 4. Rates of Solicited Adverse Reactions on Days 0-7 After Each Vaccination in Children 12 Years to <18 Years of Age, by Dose and Treatment Group, Study 1[§], Philippines

	Post Dose 1 (% of subjects)		**Post Dose 2 (% of subjects)**
Injection Site Reactions	**IXIARO* (N=240‡)**	**Havrix (N=80‡)**	**IXIARO* (N=238‡)**
Pain	15.0	12.5	6.7
Itching	0.8	0.0	0.4
Tenderness	10.0	13.8	4.6
Hardening	1.3	0.0	0.4
Swelling	0.4	1.3	0.8
Redness	0.8	6.3	3.8
Solicited Systemic Reactions			
Irritability	2.1	1.3	0.0
Nausea	2.1	1.3	0.0
Vomiting	1.3	0.0	0.0
Diarrhea	0.4	2.5	0.0
Flu-like symptoms	3.3	7.5	1.3
Excessive fatigue	2.5	1.3	0.4
Muscle pain	2.9	5.0	1.3
Rash	0.8	1.3	0.0
Headache	4.6	5.0	3.4
Loss of appetite	2.1	2.5	0.4
Fever ≥37.7°C (≥99.9°F)	3.8	6.3	5.0
37.7-38.6°C (99.9-101.5°F)	3.3	3.8	3.8
38.7-39.3°C (101.6-102.7°F)	0.4	1.3	1.3
39.4-40.5°C (102.8-104.9°F)	0.0	1.3	0.0
>40.5°C (>104.9°F)	0.0	0.0	0.0

[§]NCT01041573

*IXIARO dose 0.5 mL on Days 0 and 28.

‡N=number of subjects with available diary card data after each dose, used as the denominator to calculate percentages.

Serious Adverse Events

There was one death due to disseminated intravascular coagulation following suspected bacterial meningitis in a 12 year old male 4 months after the second dose of IXIARO. Forty serious adverse events (SAEs) were reported during the 7 month study period. Twenty-three subjects (1.6%) who received IXIARO, 1 subject (1.6%) who received Prevnar and 10 subjects (2.5%) who received HAVRIX experienced an SAE. Some subjects experienced more than one SAE. The SAEs occurring most frequently in all study groups were febrile convulsions. A total of 12 febrile convulsions were reported (9 of them as SAEs), in 8 subjects (1.0% of children below the age of 3 years) receiving IXIARO, 3 subjects (1.4% of children below the age of 3 years) receiving HAVRIX and 1 subject (1.6%) receiving Prevnar. All febrile convulsions occurred in children below the age of 3 years. Onset of febrile convulsions ranged from 2 days to >5 months after doses of IXIARO with no apparent temporal clustering, 4 weeks after Prevnar and 9 days to >16 weeks after HAVRIX.

Adverse Events in a Pediatric Trial of IXIARO Days 0 and 28 Primary Series in Children and Adolescents Traveling from Non-Endemic Areas:

The safety of the IXIARO Days 0 and 28 primary series was evaluated in an uncontrolled, open-label clinical trial conducted in the United States, Europe and Australia in healthy children and adolescents with planned travel to JEV-endemic areas (Study 2)[2]. IXIARO (0.25 mL dose for

children 2 months to <3 years of age, 0.5 mL dose for children and adolescents 3 to <18 years of age) was administered by intramuscular injection on Day 0 and Day 28. Adverse events were recorded as in Study 1[1]. An analysis of safety included 100 subjects (mean age:11.6 years, range 9 months to <18 years; 53.0% female; race: White: 83.0%, Asian: 13.0%, Black: 3.0%). Solicited adverse reactions in Study 2[2] were generally reported less frequently than in Study 1[1] and were generally less frequent following dose 2 compared to dose 1. The most common solicited adverse reactions (>10%) following either 0.25 mL dose (N=12) were injection side redness (25%) and diarrhea (17%) and following either 0.5 mL dose (N = 88) were injection site tenderness (50%), injection site pain (25%), muscle pain (31%), and excessive fatigue (11%).

Adverse Events in a Pediatric Trial of IXIARO Booster Dose in a JEV Endemic Country:

A subset of 300 subjects who completed primary immunization with IXIARO in Study 1[1] were enrolled in an open label follow-on trial (Study 3)[3] and randomized 1:1 to receive a single IXIARO booster dose (0.25 mL for ages 14 months to <3 years or 0.5 mL for ages 3 to <18 years) vs. no booster dose at 11 months after completion of the IXIARO primary series. Adverse events were recorded as in Study 1[1], with follow-up through 24 months after the booster dose. Analysis of safety was carried out using the safety population of 150 subjects (mean age 5.5 years, range 2 months to <18 years; 49.5% female race: Asian: 100%). Solicited adverse reactions were generally reported less frequently following the booster dose than following primary series vaccinations. The most common solicited adverse reactions were fever (7%) following the 0.25 mL booster dose (N=81) and injection site pain (9%) and fever (9%) following the 0.5 mL booster dose (N=67).

Clinical Studies in Adults 18 Years of Age and Older:

Overall, 4,446 healthy adults 18 to 86 years of age received at least one dose of IXIARO and were followed-up for safety for at least 6 months after the first dose in eight clinical studies [4, 5, 6, 7, 8, 12, 13, 14] conducted in North America, Europe, Australia and New Zealand.

Adverse Events in a Clinical Trial Comparing IXIARO Days 0 and 28 Primary Series to an Inactive Control in Adults:

The safety of the IXIARO Days 0 and 28 primary series was evaluated in a randomized, controlled, double-blind clinical trial in healthy male and female subjects ≥18 years of age (Study 4)[4]. IXIARO was compared to a control: Phosphate Buffered Saline containing 0.1% aluminum hydroxide [PBS + $Al(OH)_3$]. A total of 2,675 subjects were randomized in a 3:1 ratio to receive either an intramuscular injection of IXIARO (0.5 mL) each on Day 0 and Day 28, or an intramuscular injection of PBS + $Al(OH)_3$ (0.5 mL) each on Day 0 and Day 28. Analysis of safety was carried out using the safety population including 1,993 subjects receiving at least one dose of IXIARO and 657 subjects receiving at least one dose of PBS + $Al(OH)_3$ (mean age: 33.8 years, range 18 to 86 years; 55.3% female; ethnicity: White: 91.7%, Asian: 1.8%, Black: 3.4%, Other: 3.0%). The IXIARO and control groups were similar with regard to demographics. Subjects recorded adverse events on a diary card for the first seven days after each vaccination. In addition, the study investigator took a medical history and performed a physical exam to evaluate for adverse events on the day of each vaccination and at a visit 4 weeks after the second vaccination.

Injection Site Reactions

Injection site reactions after IXIARO were compared to reactions after PBS + $Al(OH)_3$. Symptoms were recorded into a subject diary for the first seven days after each injection, and the injection site was assessed by the investigator at each visit. The rates of injection site reactions are shown in Table 5. Most injection site reactions (>90%) were mild to moderate.

Table 5. Rates of Injection Site Solicited Adverse Reactions* After IXIARO or Control [PBS + $Al(OH)_3$], Administered on Days 0 and 28 to Adults Residing in Non-Endemic Areas, Safety Population With Evaluable Diary Cards, Study 4§

	Post Dose 1 (% of subjects†)		Post Dose 2 (% of subjects†)		Post Dose 1 or Dose 2 (% of subjects†)	
Adverse Reaction	**IXIARO N‡=1963**	**PBS + $Al(OH)_3$ N‡=645**	**IXIARO N‡=1951**	**PBS + $Al(OH)_3$ N‡=638**	**IXIARO N‡=1963**	**PBS + $Al(OH)_3$ N‡=645**
Any Reaction	48.5	47.7	32.6	32.2	55.4	56.2
Pain	27.7	28.2	17.7	18.2	33.0	35.8
Tenderness	28.8	26.9	22.5	18.1	35.9	32.6
Erythema	6.8	5.4	4.6	4.1	9.6	7.4
Induration	4.8	5.3	4.0	3.0	7.5	7.4
Edema	2.4	3.3	2.3	1.6	4.2	4.6
Pruritus	2.6	3.3	1.6	1.9	3.8	4.5

§NCT00605085

* Injection site reactions were assessed for 7 days after each dose.

† Denominators used to calculate percentages are based on the number of evaluable diary card entries (defined as documented presence on *any day* [i.e., entry of "yes"] or absence on *all days* [i.e., entry of "no"]) for each individual symptom and observation period.
‡N=number of subjects who returned diary cards after each dose.

Systemic Adverse Events

Overall, the percentage of subjects who experienced at least one adverse event during the study period was 58.9% in the IXIARO group compared to 56.6% in the PBS + $Al(OH)_3$ group. Adverse events of any severity grade occurring with an incidence of ≥1% of subjects are shown in Table 6. Most adverse events (>90%) were mild to moderate.

Table 6. Rates of Common Solicited and Unsolicited Systemic Adverse Events* in Adults Residing in Non-Endemic Areas After IXIARO or Control [PBS + Al(OH)$_3$] Administered on Days 0 and 28, Safety Population, Study 4[§]

Adverse Event	Post Dose 1 (Day 0 to Day 28) % of subjects		Post Dose 2 (Day 28 to Day 56) % of subjects		Post Dose 1 or Dose 2 (Day 0 to Day 56) % of subjects	
	IXIARO N‡=1993	PBS + Al(OH)$_3$ N‡=657	IXIARO N‡=1968	PBS + Al(OH)$_3$ N‡=645	IXIARO N‡=1993	PBS + Al(OH)$_3$ N‡=657
Headache†	21.6	20.2	13.4	13.0	27.9	26.2
Myalgia†	13.3	12.9	5.6	5.3	15.6	15.5
Fatigue†	8.6	8.7	5.2	5.9	11.3	11.7
Influenza-like Illness†	8.2	8.5	5.8	4.3	12.3	11.7
Nausea†	4.7	5.3	2.6	3.7	6.6	7.5
Nasopharyngitis	2.3	1.8	2.6	2.3	4.7	4.0
Fever†	1.9	2.1	1.5	1.7	3.2	3.0
Rhinitis	1.0	0.8	0.5	0.6	1.4	1.4
Upper Respiratory Tract Infection	0.9	0.9	0.8	0.9	1.7	2.0
Back Pain	0.8	0.9	0.6	0.2	1.3	1.1
Pharyngolaryngeal Pain	0.8	0.9	1.0	0.5	1.6	1.4
Rash†	0.8	0.9	0.7	0.8	1.3	1.5
Diarrhea	0.8	0.8	0.7	0.3	1.5	1.1
Cough	0.8	0.8	0.6	0.6	1.2	1.2
Vomiting†	0.6	0.8	0.8	0.9	1.4	1.7

[§]NCT00605085

*The adverse events in this table are those observed at an incidence of ≥1% in the IXIARO or PBS + Al(OH)$_3$ groups.

† These symptoms were solicited in a subject diary card. Percentages also include unsolicited events that occurred after the 7 day period covered by the diary card.

‡N=number of subjects in the safety population (subjects treated with at least one dose) who received the respective dose

Serious Adverse Events

No deaths occurred during this trial. Sixteen serious adverse events (SAE) were reported during the study period. Ten subjects (0.5%) who received IXIARO and 6 subjects (0.9%) who received PBS + Al(OH)$_3$ experienced a SAE. None of the SAEs in the IXIARO group were assessed as related to IXIARO.

Adverse Events in a Clinical Trial Comparing IXIARO Days 0 and 28 Primary Series to JE-VAX Days 0, 7, and 28 Primary Series in Adults:

The safety of IXIARO compared to another U.S.-licensed inactivated JE vaccine (JE-VAX) was evaluated in a randomized, double-blind clinical trial in subjects ≥18 years of age (Study 5)[5].

No deaths occurred during this trial. One serious adverse event occurred in this trial in a subject with a history of myocardial infarction (MI) who experienced a MI three weeks after receiving the 2nd dose of IXIARO. The most common adverse events after immunization occurring in ≥1% of subjects were headache, myalgia, fatigue, influenza-like illness, nausea, nasopharyngitis, fever, pharyngolaryngeal pain, cough, rash, diarrhea, sinusitis, upper respiratory tract infection, back pain, migraine, vomiting and influenza, which occurred with similar frequency in both treatment groups. Local injection site reactions solicited in diary cards for 7 days after each vaccination were observed at a rate of 54% in the IXIARO group (N=428) compared to a rate of 69.1% in the JE-VAX group (N=435).

Adverse Events in a Clinical Trial Investigating IXIARO Days 0 and 7 Primary Series Administered Concomitantly with Rabies Vaccine to Adults 18 through 65 years of Age:

The safety of the IXIARO Days 0 and 7 primary series administered concomitantly with an inactivated rabies vaccine (Rabipur, marketed in the U.S. as RabAvert) was evaluated in a randomized, observer-blind, controlled clinical trial in subjects 18 through 65 years of age (Study 6[6]). A total of 661 subjects were randomized into four groups: Group 1, IXIARO on Days 0 and 28 and rabies vaccine on Days 0, 7, and 28 (N=167); Group 2, IXIARO on Days 0 and 7 and rabies vaccine on Days 0, 3, and 7 (non-U.S.-licensed schedule, N=217); Group 3, IXIARO alone on Days 0 and 28 (N=56); and Group 4, rabies vaccine alone on Days 0, 7, and 28 (N=221). The groups were similar with regard to demographics (mean age 36.7 years, range 18 to 65 years; 54% female; ethnicity: 98% White, <1% Black, <1% Asian, and <1% Other for Study 6 overall). Solicited adverse events were collected via diary cards for seven days after each study vaccination, unsolicited adverse events were assessed at clinic visits through Day 56, and serious adverse events were assessed through Day 365. Analysis of safety was carried out using the safety population including subjects receiving at least one study vaccination and with evaluable safety data.

Table 7 provides an overview of solicited injection-site and systemic adverse reactions following any IXIARO vaccination. Solicited injection-site and systemic adverse reactions were usually mild to moderate in intensity, with lower rates following dose 2 compared to dose 1.

Table 7: Rates of Solicited Adverse Reactions (Days 0-7 after any Vaccination) following Two Administration Schedules of IXIARO Primary Series With or Without Concomitant Rabies Vaccine* in Subjects 18 through 65 Years of Age, Safety Population, Study 6[§]

Solicited IXIARO Injection-Site Adverse Reactions	IXIARO (Days 0, 7) +Rabies Vaccine* (% of subjects) N=217	IXIARO (Days 0, 28) +Rabies Vaccine* (% of subjects) N=166	IXIARO (Days 0, 28) (% of subjects) N=56
Pain	55.3	59.6	53.6
Erythema	21.7	17.5	19.6
Induration	12.4	9.6	14.3
Solicited Systemic Adverse Reactions			
Fatigue	42.9	32.5	33.9
Headache	40.6	37.3	30.4
Myalgia	34.6	30.1	16.1
Nausea	13.8	10.8	14.3
Arthralgia	13.4	7.8	5.4
Loss of Appetite	11.1	11.4	16.1
Temperature ≥38ºC	1.8	1.8	0.0

[§]NCT01662440
*Rabipur (marketed in the U.S. as RabAvert) was administered on Days 0, 3, and 7 (non-U.S.-licensed schedule) to subjects randomized to IXIARO Days 0 and 7 primary series and on Days 0, 7, and 28 to subjects randomized to IXIARO Days 0 and 28 primary series.
N=number of subjects

Serious Adverse Events
Eight subjects who received IXIARO reported at least one SAE, only one of which (eyelid edema/generalized pruritus the same day following IXIARO alone) was assessed as related to IXIARO.

Adverse Events in a Clinical Trial Investigating a Booster Dose of IXIARO in Adults:

The safety of a booster dose of IXIARO administered 14 months after completion of the primary series was evaluated in an open-label, uncontrolled study in subjects ≥18 years of age (Study 7)[7].

Within 28 days of booster vaccination, adverse events were reported by 35.4% of subjects (N=198). Within 12 months of booster vaccination, subjects who experienced at least one adverse event were 56.1%. Injection site reactions were reported in the subject diary for 30.8% of subjects within 7 days of booster vaccination. Adverse events considered by the investigators to be treatment-related were recorded for 11.6% of subjects (these related events were all observed within one month after the booster dose administration).

The most common injection site reactions (>10% of subjects) were pain (12.8%) and tenderness (19.2%); the most common systemic adverse events (>10%) were nasopharyngitis (15.2%) and headache (11.1%).

Safety in Concomitant Use with the Hepatitis A Vaccine, HAVRIX in Adults

The safety of the IXIARO Days 0 and 28 primary series when administered concomitantly with inactivated Hepatitis A Virus vaccine (HAVRIX) was evaluated in a controlled trial (Study 8)[8] in which subjects ≥18 years of age were assigned randomly to one of three treatment groups: Group A (N=62) received IXIARO + HAVRIX; Group B (N=65) received IXIARO + control [PBS + $Al(OH)_3$]; Group C (N=65) received HAVRIX + control [PBS + $Al(OH)_3$]. One serious adverse event occurred in this trial in a subject with a history of alcoholism and seizure disorder who experienced a seizure three weeks after receiving the 2nd dose of IXIARO + control.

The percentage of subjects who experienced at least one adverse event was as follows: Group A: 38.7%; Group B: 41.5%; Group C: 47.7%. The most frequently reported injection site reaction on the day of the first vaccination in all three groups was injection site pain in 59.0% of subjects in Group A, in 48.4% of subjects in Group B and in 48.4% of subjects in Group C.

6.2 Post-Marketing Experience

The following additional adverse reactions have been identified during post approval use of IXIARO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to the vaccine.

Nervous system disorders: Paraesthesia, neuritis, syncope.

7 DRUG INTERACTIONS

7.1 Use with Immunosuppressive Therapies

Immunosuppressive therapies may decrease the immune response to IXIARO [*See Warnings and Precautions (5)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Healthcare practitioners are encouraged to report use in pregnant women to the distributor, Valneva USA, Inc., at 844-349-4276 (8443-IXIARO).

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. There are no adequate and

well-controlled studies of IXIARO in pregnant women, and human data available from clinical trials and post-marketing experience with IXIARO are insufficient to establish the presence or absence of drug-associated risk during pregnancy.

One developmental toxicity study was performed in female rats administered IXIARO prior to mating and during gestation. The dose was 0.5 mL on each occasion (a single human dose is 0.25 mL or 0.5 mL). The study revealed no evidence of harm to the fetus due to IXIARO

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk: Miscarriages and intrauterine infection have been reported following maternal infection with JEV.

Data
Animal data
In a developmental toxicity study, female rats were administered IXIARO by intramuscular injection 3 weeks and one week prior to mating and on gestation day 6. The dose was 0.5 mL on each occasion (a single human IXIARO dose is 0.25 mL or 0.5 mL). No effects on pre-weaning development up to postnatal day 18 were observed. There were no vaccine-related fetal malformations or variations.

8.2 Lactation

Risk Summary

It is not known if IXIARO is excreted in human milk. Data are not available to assess the effects of IXIARO on the breastfed child or on milk production /excretion.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IXIARO and any potential adverse effects on the breastfed child from IXIARO or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

Safety and effectiveness of IXIARO have not been established in infants younger than 2 months of age. Safety and effectiveness of IXIARO have been established in the pediatric population 2 months of age and older [*See Adverse Reactions* (6) *and Clinical Studies* (14)].

8.5 Geriatric Use

Clinical studies of IXIARO did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger subjects. In a study that included 24 subjects ≥65 years of age who received IXIARO per protocol (Study 8)[8], the proportion of these subjects achieving a JEV neutralizing antibody titer ≥1:10 at 28 days after the second dose of IXIARO was 95.8% (geometric mean titer: 255.2).

In subjects 65 years of age and older who had been vaccinated in any of five trials [4, 5, 8, 12, 14] included in a pooled dataset (N=161) adverse events were reported in 61.9% (73/118) of subjects in the IXIARO group, 57.7% (15/26) in the JE-VAX group, and 70.6% (12/17) in the control [PBS + $Al(OH)_3$] group. Serious adverse events (SAE) were experienced by four subjects (3.4%) who received IXIARO, no subjects who received JE-VAX, and one subject (5.9%) who received the control [PBS + $Al(OH)_3$]. None of the SAEs occurring in the IXIARO group were assessed as related to IXIARO.

11 DESCRIPTION

IXIARO, Japanese Encephalitis Vaccine, Inactivated, Adsorbed is a sterile suspension for intramuscular injection. Each 0.5 mL dose of vaccine contains 6 antigen units of purified,

inactivated JEV and approximately 250 mcg of aluminum hydroxide. The appearance of the liquid is a white, opaque, non-uniform suspension which becomes homogeneous upon shaking.

IXIARO is a vaccine prepared by propagating JEV strain SA_{14}-14-2 in Vero cells. Multiple viral harvests are pooled, clarified and concentrated. The virus suspension is treated with protamine sulfate to remove contaminating DNA and proteins. The resulting partially purified virus is processed through a sucrose density gradient centrifugation step and fractionated. Each fraction is analyzed for the presence of virus, and fractions with the highest virus activity are pooled to give a purified virus suspension. The purified virus is then inactivated by treatment with formaldehyde. The preparation is adjusted to a specified antigen content and formulated by addition of aluminum hydroxide.

The formulated bulk vaccine is filled into syringes, at a volume of 0.5 mL per syringe. From the manufacturing process, IXIARO also contains: formaldehyde (not more than 200 ppm), bovine serum albumin (not more than 100 ng/mL), host cell DNA (not more than 200 pg/mL), sodium metabisulphite (not more than 200 ppm), host cell protein (not more than 100 ng/mL), and protamine sulfate (not more than 1µg/mL). No preservatives, stabilizers, or antibiotics are added to the formulation.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Japanese encephalitis is a disease caused by the mosquito-borne Japanese encephalitis virus (JEV). IXIARO acts by inducing antibodies that neutralize live JEV. Accumulated data from animal studies, clinical trials of other JE vaccines, and human epidemiological studies, suggest that a virus neutralizing antibody response, as measured *in vitro* in a 50% plaque-reduction neutralization antibody test ($PRNT_{50}$) with a threshold titer of $\geqslant$1:10, provides evidence of protective immunity[9, 10]. The evaluation of vaccine effectiveness of IXIARO was therefore based on neutralizing antibody response using a threshold $PRNT_{50}$ titer of $\geq$1:10.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

IXIARO has not been evaluated for carcinogenic or mutagenic potential. IXIARO was found to have no effect on fertility of female rats [*See Use in Specific Populations* (8.1)]. The effect of IXIARO on male fertility has not been evaluated.

14 CLINICAL STUDIES

14.1 Immunogenicity of IXIARO in Children and Adolescents

Immunogenicity of IXIARO Days 0 and 28 Primary Series in Children and Adolescents from a JEV-Endemic Country:

The immunogenicity of the IXIARO Days 0 and 28 primary series was evaluated in a subgroup of children included in a randomized, controlled, open-label clinical trial in healthy children conducted in the Philippines (Study 1)[1] in which the safety of IXIARO was compared to control vaccines: HAVRIX (Hepatitis A vaccine, pediatric 720 EL.U./0.5 mL formulation) and Prevnar (Pneumococcal 7-valent Conjugate Vaccine [Diphtheria CRM_{197} protein]). Subjects in the IXIARO treatment arm received intramuscular doses on Day 0 and Day 28. A total of 396 subjects from the group receiving an age-appropriate dosage of IXIARO (0.25 mL for infants and children 2 months to <3 years of age or 0.5 mL for individuals 3 to <18 years of age) were randomized in an age-stratified scheme into the immunogenicity subgroup (mean age: 7.7 years; 49.6% female; ethnicity: 100% Asian). [*See Adverse Reactions (6.1)*]

The immunogenicity evaluation included the proportion of subjects with $PRNT_{50}$ titer ≥1:10 and $PRNT_{50}$ geometric mean titer (GMT) at Day 56 and Month 7. The JEV-neutralizing antibody responses elicited by IXIARO in the Intent-to-Treat population (defined as all subjects who received at least one dose of IXIARO) are presented in Table 8.

Table 8. JEV-Neutralizing Antibody Response After IXIARO* Days 0 and 28 Primary Series Among Children 2 Months to <18 Years of Age Residing in the Philippines, Intent-To-Treat Population, Study 1[§]**

Age Group	2 months – <6 months	6 months – <12 months	1 year – <3 years	3 years - <12 years	12 years - <18 years
Time Point	**Proportion of Subjects with $PRNT_{50}$ Titer ≥1:10 (n/N) [95% CI]**				
Pre-Vaccination	**30%** (3/10) [10.8%, 60.3%]	**0%** (0/20) [0.0%, 16.1%]	**3.2%** (4/125) [1.3%, 7.9%]	**16.8%** (17/101) [10.8%, 25.3%]	**45.7%** (64/140) [37.7%, 54.0%]
Day 56 (28 days after dose 2)	**100%** (9/9) [70.1%, 100.0%]	**100%** (19/19) [83.2%, 100.0%]	**99.2%** (119/120) [95.4%, 99.9%]	**100.0%** (100/100) [96.3%, 100.0%]	**100%** (137/137) [97.3%, 100.0%]
Month 7 (6 months after dose 2)	**100%** (10/10) [72.2%, 100.0%]	**100%** (18/18) [82.4%, 100.0%]	**85.5%** (106/124) [78.2%, 90.6%]	**91.0%** (91/100) [83.8%, 95.2%]	**97.1%** (133/137) [92.7%, 98.9%]
Time Point	**Geometric Mean Titers◊ (N) [95% CI]**				
Pre-Vaccination	**8.4** (10) [4.3, 16.7]	**5.0** (20) [5.0, 5.0]	**5.5** (124) [5.0, 6.1]	**6.5** (101) [5.8, 7.4]	**13.1** (140) [10.7, 16.1]
Day 56 (28 days after dose 2)	**687.4** (9) [263.2, 1795.1]	**377.8** (19) [210.3, 678.8]	**258.9** (121) [214.4, 312.6]	**213.7** (100) [175.6, 260.0]	**175.6** (137) [147.8, 208.7]
Month 7 (6 months after dose 2)	**159.3** (10) [110.0, 230.7]	**64.0** (18) [39.4, 104.1]	**38.9** (125) [31.8, 47.7]	**43.6** (100) [35.6, 53.4]	**86.6** (137) [70.7, 106.0]

[§]NCT01041573

*Infants and children ≥2 months to <3 years of age received two 0.25 mL doses administered on Days 0 and 28. Individuals 3 years of age and older received two 0.5 mL doses administered on Days 0 and 28.

**The Intent to Treat population consisted of all subjects who received at least one dose of IXIARO.

N=number of subjects with data available

n=number of subjects with a $PRNT_{50}$ titer ≥1:10

◊Reciprocal titers <10 were imputed to 5.

Antibody Persistence Following IXIARO Days 0 and 28 Primary Series and Immunogenicity of IXIARO Booster Dose in Children and Adolescents from a JEV-Endemic Country:

A subset of 300 subjects who completed primary immunization with IXIARO in Study 1[1] were enrolled in an open label follow-on trial (Study 3)[3] and randomized 1:1 to receive a single IXIARO booster dose (0.25 ml for ages 14 months to <3 years or 0.5 ml for ages 3 to <18 years) vs. no booster dose at 11 months after completion of the IXIARO primary series. Demographics were similar for the booster and non-booster groups and overall included a mean age at booster

dose (or second visit for non-booster group) of 5.3 years (range 1.2 - 17.3 years), 48.0% female, and race 100% Asian. Immunogenicity evaluations were conducted in the Intent to Treat population of all subjects as randomized and included the proportions of subjects with $PRNT_{50}$ titer ≥1:10 and $PRNT_{50}$ GMTs at Month 12, Month 13 (booster dose group only), Month 24 and Month 36 after the initiation of the IXIARO primary series. As shown in Table 9, the booster dose led to an increase in $PRNT_{50}$ GMTs, and the proportion of subjects with $PRNT_{50}$ titer ≥1:10 remained at 100% two years after the booster.

Table 9: Persistence of JEV-Neutralizing Antibody Response With and Without IXIARO Booster Dose Among Children 14 Months to <18 Years of Age Residing in the Philippines, Intent-To-Treat Population, Study 3[§]**

	No Booster Dose	**0.25 mL Booster Dose (14 months to <3 years of age)**	**0.5 mL Booster Dose (3 to <18 years of age)**
Time point	**Proportion of Subjects with $PRNT_{50}$ Titer ≥1:10 (n/N) [95% CI]**		
Month 12 (11 months after completion of primary series*)	89.9% (134/149) [84.1%, 93.8%]	97.5% (79/81) [91.4%, 99.3%]	89.6% (60/67) [80.0%, 94.4%]
Month 13 (12 months after completion of primary series*)	NA	100.0% (81/81) [95.5%, 100%]	100.0% (67/67) [94.6%, 100.0%]
Month 24 (23 months after completion of primary series*)	89.0% (130/146) [82.9%, 93.1%]	100.0% (80/80) [95.4%, 100.0%]	100.0% (67/67) [94.6%, 100.0%]
Month 36 (35 months after completion of primary series*)	90.1% (128/142) [84.1%, 94.0%]	100.0% (76/76) [95.2%, 100.0%]	100.0% (67/67) [94.6%, 100.0%]
	Geometric Mean Titers◊ (N) [95% CI]		
Month 12 (11 months after completion of primary series*)	45.5 (149) [37.8, 54.8]	67.3 (81) [54.0, 83.8]	40.4 (67) [30.5, 53.5]
Month 13 (12 months after completion of primary series*)	NA	2910.8 (81) [2235.1, 3791.0]	1365.9 (67) [987.6, 1889.0]
Month 24 (23 months after completion of primary series*)	49.8 (146) [40.6, 61.1]	572.3 (80) [409.8, 799.4]	302.1 (67) [213.3, 428.0]
Month 36 (35 months after completion of primary series*)	59.4 (142) [48.4, 72.8]	427.5 (76) [313.0, 583.8]	279.6 (67) [200.6, 389.9]

[§]NCT01296360
*IXIARO primary series administered on Days 0 and 28.
**The Intent to Treat Population consisted of all subjects as randomized.
N=number of subjects with data available
n=number of subjects with a $PRNT_{50}$ titer ≥1:10
NA = not assessed
◊Reciprocal titers <10 were imputed to 5.

Immunogenicity of IXIARO Days 0 and 28 Primary Series in Children 2 Months to < 18 Years of Age Traveling from Non-Endemic Areas:

The immunogenicity of the IXIARO Days 0 and 28 primary series 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 (Study 2)[2] IXIARO (0.25 mL dose for infants and children 2 months to <3 years of age, 0.5 mL dose for children and adolescents 3 to <18 years of age) was administered by intramuscular injection on Day 0 and Day 28. The immunogenicity analysis population included 64 out of 100 enrolled subjects (5 subjects ages 2 months to <3 years and 59 subjects ages 3 to <18 years) and was 54.7% female with race 82.8% White, 3.1% Black, and 14.1% Asian. All 64 subjects were seronegative for JEV-neutralizing antibodies pre-vaccination, and the proportions of subjects with $PRNT_{50}$ Titer ≥1:10 at 1 month and 6 months after completion of the primary series were 100% (62/62) and 91.2% (31/34), respectively. Post-vaccination JEV-neutralizing GMTs by age group were similar to those among children vaccinated with IXIARO in a study conducted in the Philippines, where JEV is endemic (see Table 8).

Twenty-three subjects from Study 2[2] (1 subject who completed the 0.25 mL dose primary series and 22 subjects who completed the 0.5 mL dose primary series) were enrolled in a follow-on study to evaluate antibody persistence (Study 9[11]**).** The proportions of subjects with $PRNT_{50}$ Titer ≥1:10 at 11 months, 23 months, and 35 months after completion of the primary series were 89.5% (17/19), 91.3% (21/23) and 89.5% (17/19) respectively. JEV-neutralizing GMTs at these time points were similar to those among children vaccinated with IXIARO in a study conducted in the Philippines, where JEV is endemic (see Table 9).

14.2 Immunogenicity of IXIARO in Adults

Immunogenicity of IXIARO Days 0 and 28 Primary Series in Adults:

Immunogenicity of the IXIARO Days 0 and 28 primary series was evaluated in a randomized, active-controlled, observer-blinded clinical trial conducted in the U.S., Germany and Austria (Study 5)[5] in 867 healthy adults 18 years of age and older (mean age: 41.3 years; 60.8% female; ethnicity: White 80.8%, Asian 0.8%, Black 13.1%, Other 5.3%). Subjects in the IXIARO treatment arm received the following schedule of three intramuscular doses: Day 0, IXIARO, Day 7, PBS + $Al(OH)_3$ (0.5 mL phosphate buffered saline with 0.1% aluminum hydroxide), and on Day 28, IXIARO. Subjects in the comparator arm received a subcutaneous dose of 1.0 mL of the US-licensed JEV vaccine, JE-VAX, on Days 0, 7 and 28. [*See Adverse Reactions (6.1)*]

The proportion of subjects with, $PRNT_{50}$ titer ≥1:10, and GMT were evaluated at Day 56 in the per protocol population which included all subjects who had no major protocol deviations and who had a $PRNT_{50}$ titer <1:10 at baseline. The neutralizing antibody responses elicited by IXIARO met predefined statistical criteria for non-inferiority compared to those induced by JE-VAX, and are presented in Table 10. All subjects were seronegative at baseline ($PRNT_{50}$ titer <1:10).

Table 10. JEV-Neutralizing Antibody Response After IXIARO* or JE-VAX* Among Adults Residing in Non-Endemic Areas, Per Protocol Population, Study 5[§]**

Proportion of Subjects with $PRNT_{50}$ Titer ≥1:10			
Time Point	IXIARO (n/N) [95% CI]	JE-VAX (n/N) [95% CI]	Rate difference [95% CI]
Day 56 (28 days after last dose)	**96.4%** (352/365) [94.0%, 97.9%]	**93.8%** (347/370) [90.9%, 95.8%]	**2.6%** [-0.5%,6.0%]†
Geometric Mean Titers◊			
Time Point	IXIARO (N¶=361) [95% CI]	JE-VAX (N¶=364) [95% CI]	GMT ratio [95% CI]
Day 56 (28 days after last dose)	**243.6** [216.4, 274.1]	**102.0** [90.3, 115.2]	2.33 [1.97, 2.75]‡

[§]NCT00604708

*IXIARO was administered on Days 0 and 28; JE-VAX was administered on Days 0, 7, and 28.

**The Per Protocol population consisted of subjects with no major protocol deviations and a $PRNT_{50}$ titer <1:10 at baseline.

† Non-inferiority was demonstrated if the lower bound of the 2-sided 95% confidence interval (CI) for the difference in proportion of subjects with $PRNT_{50}$ titer ≥1:10 (IXIARO minus JE-VAX) was >-10% at Day 56.

‡ Non-inferiority was demonstrated if the lower bound of the 2-sided 95% CI for the GMT ratio (IXIARO /JE-VAX) was >1/1.5 at Day 56.

n=number of subjects with a $PRNT_{50}$ titer ≥1:10

N=number of subjects in the Per Protocol Population

¶N=Number of subjects with immunogenicity data

◊Reciprocal titers <10 were imputed to 5.

Temporal Evaluation of Immunogenicity of IXIARO During the Days 0 and 28 Primary Vaccination Series in Adults:

In a randomized, observer-blinded clinical study in 374 healthy adults 18 years of age and older (Study 10[12]), the immunogenicity of IXIARO was evaluated on days 10, 28, 35, and 56 during the vaccination period. The proportion of subjects with $PRNT_{50}$ titer ≥1:10 at each time point for the subjects randomized to the standard dosing regimen (IXIARO on days 0 and 28) are displayed in Table 11.

Table 11. JEV-Neutralizing Antibody Response During the Primary Vaccination Series (IXIARO on Days 0 and 28) Among Adults Residing in Non-Endemic Areas, Per Protocol Population*, Study 10[§]

Time Point	**Proportion of Subjects with $PRNT_{50}$ Titer ≥1:10 (n/N) [95% CI]**
Day 10 (10 days after vaccine dose 1)	**21.1%** (24/114) [13.6%, 28.5%]
Day 28 (28 days after vaccine dose 1)	**39.8%** (45/113) [30.8%, 48.8%]
Day 35 (7 days after vaccine dose 2)	**97.3%** (110/113) [94.4%, 100.0%]
Day 56	**97.3%** (110/113)

(28 days after vaccine dose 2)	[94.4%, 100%]

§NCT00595790
*The Per Protocol population consisted of all subjects with no major protocol deviations
n=number of subjects with a $PRNT_{50}$ titer ≥1:10
N=number of subjects with immunogenicity data

Persistence of Neutralizing Antibody Response Following the Days 0 and 28 Primary Vaccination Series in Adults:

The persistence of JEV-neutralizing antibody was evaluated in a subgroup of adult subjects recruited for follow-up after participation in one of two clinical trials (Study 4 and Study 5)[4, 5]. In the Intent-to-Treat population of subjects randomized to vaccination with IXIARO (N=181) and in the population of subjects who intended to stay in the study until month 36 (ITT36, N = 152), the proportion of subjects with $PRNT_{50}$ titer ≥1:10 at 6, 12, 24 and 36 months after initiation of the two-dose series were 95% [95% CI 90.8%, 97.4%], 83.4% [95% CI 77.3%, 88.1%] , 81.8% [95% CI 75.5%, 86.7%] and 84.9% [95% CI 78.3%, 89.7%], respectively. Geometric mean titers (GMT) at 6, 12, 24 and 36 months after initiation of the two-dose series were 83.5 [95% CI 70.9, 98.4], 41.2 [95% CI 34.4, 49.3], 44.3; [95% CI 36.7, 53.4] and 43.8 [95% CI 36.5, 52.6], respectively.

In another study with 116 adults who completed the Days 0 and 28 IXIARO primary immunization series (Study 11[13]) the proportions of subjects with $PRNT_{50}$ titers ≥1:10 at 11 and 23 months after completion of the primary series were 58.3% [95% CI 49.1%, 66.9%] and 48.3% [95% CI 39.4%, 57.3%], respectively, and GMTs were 18.0 [95% CI 14.3, 22.6] and 16.2 [95% CI 12.6, 20.8].

Immunogenicity of IXIARO (Days 0 and 7 Primary Series and Days 0 and 28 Primary Series) with Concomitant Rabies Vaccine in Adults 18 through 65 Years of Age:

The immunogenicity of IXIARO (Days 0 and 7 primary series and Days 0 and 28 primary series) administered concomitantly with an inactivated rabies vaccine (Rapipur, marketed in the U.S. as RabAvert) was evaluated in a randomized, observer-blind, controlled clinical trial (Study 6)[6] in 661 subjects 18 through 65 years of age [*See Adverse Reactions (6.1)]*. Antibody responses following the concomitant vaccination regimens were compared to antibody responses following vaccination with IXIARO alone (Days 0 and 28 primary series) or rabies vaccine alone (Days 0, 7, and 28). JEV-neutralizing antibody responses are presented in Table 12.

Table 12. JEV-Neutralizing Antibody Responses Following IXIARO Days 0 and 7 Primary Series Administered With Concomitant Rabies Vaccine* and IXIARO Days 0 and 28 Primary Series Administered With or Without Concomitant Rabies Vaccine*, Per Protocol Population, Study 6[§]**

Vaccination Schedule	IXIARO (Days 0, 7) +Rabies Vaccine*	IXIARO (Days 0, 28) +Rabies Vaccine*	IXIARO (Days 0, 28)
Time Point	**Proportion of Subjects with $PRNT_{50}$ Titer ⩾1:10 (n/N) [95% CI]**		
Pre-Vaccination	6% (13/215) [3%, 10%]	1% (2/165) [0%, 4%]	9% (5/55) [3%, 20%]
7 days after IXIARO dose 2	99% (206/209) [96%, 100%]	99% (156/157) [97%, 100%]	100% (47/47) [92%, 100%]
28 days after IXIARO dose 2	99% (203/206) [96%, 100%]	100% (157/157) [98%, 100%]	100% (49/49) [93%, 100%]
>300 days[†] after IXIARO dose 2	94% (188/199) [90%, 97%]	86% (132/154) [79%, 91%]	88% (42/48) [75%, 95%]
	Geometric Mean Titers◊ (N) [95% CI]		
Pre-Vaccination	5.6 (215) [5.4, 5.9]	5.1 (165) [4.8, 5.4]	5.7 (55) [5.2, 6.3]
7 days after IXIARO dose 2	715 (209) [608, 842]	292 (157) [247, 346]	376 (47) [277, 510]
28 days after IXIARO dose 2	690 (206) [595, 801]	299 (157) [254, 352]	337 (49) [252, 451]
>300 days[†] after IXIARO dose 2	117 (199) [100, 137]	39 (154) [33, 47]	39 (48) [28, 54]

[§]NCT01662440

*Rabipur (marketed in the U.S. as RabAvert) was administered on Days 0, 3, and 7 (non-U.S.-licensed schedule) to subjects randomized to IXIARO Days 0 and 7 primary series and on Days 0, 7, and 28 to subjects randomized to IXIARO Days 0 and 28 primary series.

**The Per-Protocol population consisted of all subjects with no major protocol violations.

[†]Day 365, end of study date.

N=number of subjects with data available, n=number of subjects with a $PRNT_{50}$ titer ≥1:10

◊Reciprocal titers <10 were imputed to 5.

Comparing the IXIARO Days 0 and 7 primary series administered concomitantly with rabies vaccine to the IXIARO Days 0 and 28 primary series administered alone, the difference in proportion of subjects with JEV-neutralizing $PRNT_{50}$ Titer ⩾1:10 at 28 days after the last IXIARO dose was -1% (97.5% CI: -4.8%, 7.9%), which met the pre-specified non-inferiority criterion that the lower bound of the 2-sided 97.5% CI be greater than -10%. The study did not include a treatment arm with IXIARO Days 0 and 7 primary series administered alone, so JEV-neutralizing antibody responses following this regimen were not available for comparison.

Comparing the IXIARO Days 0 and 28 primary series administered concomitantly with rabies vaccine to the IXIARO Days 0 and 28 primary series administered alone, the JEV-neutralizing $PRNT_{50}$ GMT ratio at 28 days after the last IXIARO dose was 0.88 (95% CI: 0.68, 1.13), which met the pre-specfied non-inferiority criterion that the lower bound of the 2-sided 95% CI be greater than 0.5.

Rabies-neutralizing antibody responses following the U.S.-licensed rabies vaccination schedule (Days 0, 7, and 28) were similar when administered alone vs. concomitantly with the IXIARO Days 0 and 28 primary series.

Delayed Completion of Primary Immunization in Adults:

The immunogenicity of a second dose of the primary series administered 11 months after dose 1 was assessed in 100 adults in a study investigating persistence of immunity following vaccination with different dose-schedules of IXIARO (Study 10)[12]. Four weeks after this delayed second dose, 99.0% of subjects (99/100) had a $PRNT_{50}$ titer ≥1:10 (GMT 504.3 [95% CI: 367.3, 692.3]). One year later, 88.5% of subjects (85/96) had a $PRNT_{50}$ titer ≥1:10 (GMT 121.0 [95% CI: 87.4, 167.6]).

Immunogenicity of IXIARO Booster Dose in Adults:

A single booster dose of IXIARO was evaluated in 198 adult subjects enrolled in an uncontrolled, open-label phase 3 study. IXIARO was administered 14 months after completion of the Days 0 and 28 primary series (Study 7)[7].The JEV neutralizing antibody responses from this study are presented in Table 13.

Table 13. JEV-Neutralizing Antibody Response Following a Booster Dose of IXIARO Administered 14 Months After Completion of the Days 0 and 28 Primary Series Among Adults Residing in Non-Endemic Areas, Intent to Treat Population*, Study 7[§]

Time Point	**% PRNT Titer ≥1:10** (n/N) [95% CI]	**Geometric Mean Titers** (N) [95% CI]
Pre-booster, Day 0	**69.2%** (137/198) [62.4%, 75.2%]	**22.5** (198) [19.0, 26.7]
Day 28	**100.0%** (198/198) [98.1%, 100.0%]	**900.1** (198) [742.4, 1091.3]
Month 6	**98.5%** (194/197) [95.6%, 99.5%]	**487.4** (197) [390.7, 608.1]
Month 12	**98.5%** (191/194) [95.6%, 99.5%]	**361.4** (194) [294.5, 443.5]

[§]NCT00595309
*The Intent to Treat population consisted of all subjects who received the booster vaccination
n=number of subjects with a $PRNT_{50}$ titer ≥1:10
N=number of subjects with immunogenicity data

The immunogenicity of an IXIARO booster dose was assessed in adult subjects in another study investigating persistence of immunity following vaccination with the IXIARO Days 0 and 28 primary series (Study 10)[12]. Subjects with $PRNT_{50}$ titers <1:10 at 11 months after completion of the primary series received a booster dose of IXIARO 11 months later (22 months after completion of the primary series). Among 27 subjects with available immunogenicity data at 4 weeks after the booster dose, the proportion of subjects with $PRNT_{50}$ titer ≥1:10 was 100% [95% CI 87.5%, 100.0%], and the GMT was 2536.7 [95% CI 1467.7, 4384.4].

Concomitant Administration of IXIARO and Hepatitis A Vaccine, HAVRIX in Adults:

The concomitant use of IXIARO with inactivated Hepatitis A Virus vaccine (HAVRIX) was evaluated in a randomized, controlled, single-blind clinical trial including 192 healthy adults 18 to 61 years of age (Study 8)[8]. Subjects were divided into three treatment groups: Group A (N=62) received IXIARO (Days 0 and 28) + HAVRIX (Day 0); Group B (N=65) received IXIARO (Days 0 and 28) + control (0.5 mL phosphate buffered saline with 0.1% aluminum hydroxide by intramuscular injection on Day 0); Group C (N=65) received HAVRIX (Day 0) + control (Day 0 and 28). Anti-JEV GMT at Day 56 in Group A met non-inferiority criteria compared to anti-JEV GMT at Day 56 in Group B. In addition, anti-HAV GMT at Day 28 in Group A met non-inferiority criteria compared to anti-HAV GMT at Day 28 in Group C. Therefore, concomitant administration of IXIARO and HAVRIX did not adversely affect immunogenicity compared to administration of either vaccine individually. Safety results regarding co-administration of IXIARO with HAVRIX are summarized in *Adverse Reactions (6.1)*.

15 REFERENCES

1. Clinical study referred to as NCT01041573 in the National Library of Medicine clinical trial database, also referred to as study IC51-323 in the Biologics License Application
2. Clinical study referred to as NCT01047839 in the National Library of Medicine clinical trial database, also referred to as study IC51-322 in the Biologics License Application
3. Clinical study referred to as NCT01296360 in the National Library of Medicine clinical trial database, also referred to as study IC51-325 in the Biologics License Application.
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5. Clinical study referred to as NCT00604708 in the National Library of Medicine clinical trial database, also referred to as study IC51-301 in the Biologics License Application.
6. Clinical study referred to as NCT01662440 in the National Library of Medicine clinical trial database, also referred to as study V49-23 in the Biologics License Application
7. Clinical study referred to as NCT00595309 in the National Library of Medicine clinical trial database, also referred to as study IC51-311 in the Biologics License Application.
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9. Hoke CH, Nisalak A, Sangawhipa N, Jatanasen S, Laorakapongse T, Innis BL, Kotchasenee S, Gingrich JB, Latendresse J, Fukai K, et al. Protection against Japanese encephalitis by inactivated vaccines. N Engl J Med. 1988 Sep 8;319(10):608-14.
10. Hombach J, Solomon T, Kurane I, Jacobson J, Wood D. Report on a WHO consultation on immunological endpoints for evaluation of new Japanese encephalitis vaccines, WHO, Geneva, 2-3 September, 2004. Vaccine. 2005;23:5205-11.
11. Clinical study, study 9 in this file, referred to as NCT00595270 in the National Library of Medicine clinical trial database, also referred to as study IC51-305 in the Biologics License Application.
12. Clinical study, study 10 in this file, referred to as NCT00595790 in the National Library of Medicine clinical trial database, also referred to as study IC51-304 in the Biologics License Application.
13. Clinical study, study 11 in this file, referred to as NCT01246479 in the National Library of Medicine clinical trial database, also referred to as study IC51-324 in the Biologics License Application.
14. Clinical study referred to as NCT00594958 in the National Library of Medicine clinical trial database, also referred to as study IC51-309 in the Biologics License Application.

16 HOW SUPPLIED / STORAGE AND HANDLING

16.1 How Supplied

IXIARO is supplied as a sterile 0.5 mL suspension in a pre-filled syringe (Type I glass) with a plunger stopper (chlorobutyl elastomer) in a pack size of 1 single-dose syringe with or without a separate needle. See *Section (2.3)* for information on preparing a 0.25 mL dose for children 2

months to <3 years of age and a 0.5 mL dose for individuals 3 years of age and older. NDC 42515-002-01.

Neither the syringe nor the packaging materials are made with natural rubber latex.

16.2 Storage and Handling

Store in a refrigerator at 2° to 8° C (35° to 46° F). **Do not freeze**.

Do not use the vaccine after the expiration date shown on the label. Store in the original package in order to protect from light. During storage, a clear liquid with a white precipitate can be observed.

17 PATIENT COUNSELING INFORMATION

Question the vaccine recipient about reactions to previous vaccines, and inform the vaccine recipient of the benefits and risks of IXIARO.

Consult current U.S. and international advisories regarding prevalence of Japanese encephalitis in specific locations. Advise the parent, guardian, or recipient that IXIARO may not fully protect everyone who gets the vaccine and that personal precautions should be taken to reduce exposure to mosquito bites (adequate clothing, use of repellents, mosquito nets).

Give the parent, guardian, or recipient the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization, and inquire about previous reactions to vaccines.

Inform the parent, guardian, or recipient of the importance of completing the immunization series.

Instruct the parent, guardian, or recipient to immediately report any signs and/or symptoms of a severe adverse reaction, including anaphylaxis (difficulty breathing, wheezing, weakness or fast heartbeat, hives).

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Patient Information about
IXIARO (pronounced "īk-sē-ah-rō")
Generic name: Japanese encephalitis vaccine, inactivated, adsorbed

Read this information about IXIARO before you are vaccinated. If you have any questions about IXIARO after reading this leaflet, ask your health care provider. This leaflet does not take the place of talking with your health care professional about IXIARO. Only your health care provider can decide if IXIARO is right for you.

What is IXIARO and how does it work?

- IXIARO is a vaccine for use in individuals 2 months of age and older to help protect against Japanese encephalitis (JE). You cannot get the disease from IXIARO.
- You will need 2 doses of the vaccine.
- You should consult your health care provider on the need for a booster dose of IXIARO
- You should still protect yourself from mosquito bites even if you have had the IXIARO vaccine.
- IXIARO may not fully protect everyone who gets the vaccine.
- IXIARO does not protect against encephalitis caused by other viruses/pathogens.
- IXIARO does not protect against other diseases transmitted by mosquitoes.

What is Japanese encephalitis virus (JEV) and what is the disease caused by JEV?
Japanese encephalitis (JE) is caused by the Japanese encephalitis virus, JEV, which is mainly found in Asia. JEV 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. JE causes death in one out of every three people with overt encephalitis. One out of two survivors develops permanent brain damage. JE acquired during pregnancy may cause intrauterine infection and miscarriage.

Who is at risk for Japanese encephalitis?

- People who live in, or travel to, areas where JEV circulates.
- Laboratory personnel who work with JEV.

Who should not get IXIARO?
You should not get IXIARO if you:

- are allergic to any of the ingredients in the vaccine. A list of ingredients can be found at the end of this leaflet.
- had an allergic reaction after getting a dose of the vaccine or any other JEV vaccine.

IXIARO is not approved for use in infants below the age of 2 months.

What should I tell my health care professional before I am vaccinated with IXIARO?
It is very important to tell your health care provider if you:

- have had an allergic reaction to a previous dose of IXIARO or any other JEV vaccine.
- have a bleeding disorder or a reduction in blood platelets, which increases risk of bleeding or bruising (thrombocytopenia) and cannot receive injections in the arm.
- have a weakened immune system, for example, due to a genetic defect or HIV infection.
- are or may be pregnant, or are breast feeding. IXIARO has not been studied in pregnant women or nursing mothers.
- currently have any illness with a fever of more than 100°F (37.8°C).
- take any medicines, even those you can buy over the counter.

How is IXIARO given?
IXIARO is given as an injection in the upper arm muscle in individuals 3 years of age and older. Infants 2 to 11 months of age are given the vaccine into the thigh. Children 12 to 35 months of age may be given the vaccine into the arm muscle (if the muscle is large enough) or into the thigh.

You will get a total of 2 doses of the vaccine. All individuals 2 months of age and older can be vaccinated as follows. :

- First dose: at a date you and your health care provider choose.
- Second dose: 28 days after the first dose.

Adults 18 to 65 years of age can also be vaccinated as follows:

- First dose: at a date you and your health care provider choose.
- Second dose: 7 days after the first dose.

Make sure that you get both doses. If you miss the second dose, your health care provider will decide when to give the missed dose. Be aware that protection is not reliable until 1 week after you receive the second dose of IXIARO.

If the second dose was administered more than 1 year ago, you should consult your health care provider on the need for a booster dose of IXIARO prior to potential re-exposure to JEV.

What are the possible side effects of IXIARO?
The most common side effects in adolescents >12 years of age and adults are headache, muscle pain and injection site reactions (e.g. pain, swelling, tenderness, redness). Nausea, skin rash, fatigue, flu-like illness, fever, irritability and loss of appetite may also occur.

The most common side effects in children below the age of 12 years are fever, irritability, diarrhea, vomiting, loss of appetite, injection site pain and injection site redness.

Contact your health care provider right away if you get any symptoms after receiving IXIARO that concern you.

Tell your health care provider if you have any of the following problems because these may be signs of an allergic reaction:

- difficulty breathing
- hoarseness or wheezing
- hives
- dizziness, weakness or fast heart beat

What are the ingredients of IXIARO?
Active Ingredient: purified inactivated Japanese encephalitis virus (JEV).

Inactive Ingredients: aluminum hydroxide and phosphate buffered saline (sodium chloride, potassium dihydrogen phosphate, disodium hydrogen phosphate).

Minute amounts of other substances remain in the vaccine as a result of the manufacturing process. Refer to the package insert for a complete list.

What else should I know about IXIARO?
This leaflet is a summary of information about IXIARO. If you would like more information, please talk to your health care professional. U.S. and international agencies (such as cdc.gov and who.int) also provide additional information about JEV and related travel advisories.

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