**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)

**DOSE AND ADMINISTRATION**
For intramuscular administration only. Complete the primary immunization series at least 1 week prior to potential exposure to JEV. (2.1, 14)

Individuals 17 years of age and older who have received a primary immunization series more than 1 year previously may be given a booster dose if ongoing exposure or re-exposure to JEV is expected. (2.1)

**DOSE FORMS AND STRENGTHS**
Suspension for injection supplied in 0.5 mL single dose syringes. (2.1)

**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. (2.1)

**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)

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- 2 DOSAGE AND ADMINISTRATION
  - 2.1 Dosage and Schedule
  - 2.2 Administration
  - 2.3 Preparation for Administration
- 3 DOSAGE FORMS AND STRENGTHS
- 4 CONTRAINDICATIONS
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*If the plunger stopper is pushed beyond the red line, do not administer the vaccine. Repeat the procedure using a new prefilled syringe.

Preparation of a 0.5 mL Dose of IXIARO for Administration to Individuals 3 Years of Age and Above:
1. Shake the prefilled 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 prefilled syringe (needle is not provided with IXIARO).

Preparation of a 0.25 mL Dose of IXIARO for Administration to Children 2 Months to <3 Years of Age:
1. Shake the prefilled 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 prefilled 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.
the vaccine may be responsible, individu-
als with a history of severe allergic reac-
tion 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 hypersensitiv-
ity reactions in some individuals. (See Description (11)). Appropriate medical care should be readily available in case of anaphylactic reaction.

5.2 Limitations of Vaccine Effectiveness

Vaccination with IXIARO may not protect all individuals.

5.3 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 reactions were redness (>15%); the most common solic-
ted systemic adverse reactions were fever (>20%), irritability (>15%) and diar-
hoea (>10%). In children 3 to <12 years of age, the most common solicited systemic adverse reac-
tion 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 com-
mon injection site reactions were pain (>25%) and tenderness (>25%); the most common solicited systemic adverse reac-
tions 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 tri-
als of a vaccine cannot be directly com-
pared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

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

Adverse Events in a Pediatric Trial Comparing IXIARO to U.S.-Licensed Control Vaccines HAVRIX and PREVNAR:

The safety of IXIARO was evaluated in a randomized, controlled, double-blind clinical trial in healthy male and female sub-
jects 2 months to <18 years of age, conducted in the Philippines, a country where Japanese Encephalitis is endemic (Study 1). IXIARO was compared to two control vaccines: HAVRIX (Hepatitis A vac-
cine, pediatric 720 ELU, 0.5 mL formulation, GlaxoSmithKline Biologicals) and Prevnar (Pneumococcal 7-valent Conju-
gate Vaccine [Diphtheria CRM™ protein, Pfizer]). A total of 1,769 subjects were ran-
domized in an age-stratified scheme in a 3:1 ratio (2:1 ratio for ages <1 year) to receive intramuscular injection of IXIARO (0.5 mL) each on Day 0 and Day 28. About 1% of subjects who received IXIARO discontinued due to adverse events.

Table 1. Subject Numbers and Dosing Schemes by Age Group (Safety Population, Study 1, Philippines)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>IXIARO* (N=1311)</th>
<th>HAVRIX (N=394)</th>
<th>PREVNAR (N=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects in Age Group ≥1 year to &lt;3 years</td>
<td>640</td>
<td>213</td>
<td>-</td>
</tr>
<tr>
<td>Subjects in Age Group ≥2 months to &lt;1 year</td>
<td>131</td>
<td>-</td>
<td>64</td>
</tr>
<tr>
<td>Subjects in Age Group ≥3 to &lt;12 years</td>
<td>300</td>
<td>103</td>
<td>-</td>
</tr>
<tr>
<td>Subjects in Age Group ≥12 to &lt;18 years</td>
<td>240</td>
<td>80</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2. 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

<table>
<thead>
<tr>
<th>Injection Site Reactions</th>
<th>IXIARO* (N=444)</th>
<th>Prevnar (N=164)</th>
<th>IXIARO* (N=444)</th>
<th>Prevnar (N=164)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenderness</td>
<td>15.0</td>
<td>13.0</td>
<td>0.8</td>
<td>3.3</td>
</tr>
<tr>
<td>Hardening</td>
<td>7.6</td>
<td>6.3</td>
<td>3.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Rash</td>
<td>11.5</td>
<td>6.3</td>
<td>3.8</td>
<td>4.9</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>3.8</td>
<td>4.9</td>
<td>3.8</td>
<td>4.9</td>
</tr>
<tr>
<td>Excessive fatigue</td>
<td>11.5</td>
<td>6.3</td>
<td>3.8</td>
<td>4.9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7.6</td>
<td>6.3</td>
<td>3.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15.0</td>
<td>13.0</td>
<td>0.8</td>
<td>3.3</td>
</tr>
<tr>
<td>Redness</td>
<td>15.0</td>
<td>13.0</td>
<td>0.8</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Clinical Studies in Adults 18 Years of Age and Older:

In five randomized, controlled clinical stud-
ies5, 6, 7, 8 conducted in North Amer-
ica, Europe, Australia and New Zealand, a total of 3,558 healthy adults 18 to 86 years of age received at least one dose of IXIARO and were followed-up for safety for 6 months after the first dose. In this pooled dataset of subjects who received IXIARO, one death occurred in a subject with metastatic lung adenocarcinoma four months after completing the two-
dose regimen. About 1% of subjects who received IXIARO experienced serious adverse events, including one case of mul-
tiple sclerosis. Approximately 1% of sub-
jects who received IXIARO discontinued due to adverse events.

Table 6. Comparison of IXIARO to a Control in Adults:

The safety of IXIARO was evaluated in a randomized, controlled, double-blind clinical trial in healthy male and female sub-
jects ≥18 years of age (Study 4). IXIARO was compared to a control: Phos-
phate 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 intra-
muscular injection of IXIARO (0.5 mL) each on Day 0 and Day 28, or an intra-
muscular injection of PBS + Al(OH)3 (0.5 mL) each on Day 0 and Day 28. Analy-
sis of safety was carried out using the safety population including 1,933 sub-
jects 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;
Serious Adverse Events
No deaths occurred during this trial. Sixteen serious adverse events (SAEs) 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. The serious adverse events occurring in the IXIARO group were as follows: Dermatomyositis, appendicitis, rectal hemorrhage, limb abscess (contralateral to the injected arm), chest pain, ovarian torsion, ruptured corpus luteal cyst, and three orthopedic injuries.

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 7. Most adverse events (>90%) were mild to moderate.

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. The injection site was assessed by the investigator at each visit. The rates of injection site reactions are shown in Table 8. Most injection site reactions (>90%) were mild to moderate.

Adverse Events in a Clinical Trial Comparing IXIARO to JE-VAX 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). 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 an 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 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 9). 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 investigator 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 (Study 7)
The safety of IXIARO when administered concomitantly with inactivated Hepatitis A Virus vaccine (HAVRIX) was evaluated in a controlled trial 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 a 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, 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.

7 DRUG INTERACTIONS

7.1 Use with HAVRIX

In one clinical trial in adults, IXIARO was administered concomitantly with HAVRIX (Hepatitis A Vaccine) [See Adverse Reactions (6) and Clinical Studies (14)]. In this trial, there was no evidence for interference with the immune response to IXIARO or to HAVRIX when HAVRIX was administered concomitantly with dose 1 of IXIARO [See Clinical Studies (14)]. Data are not available on concomitant administration of IXIARO with other US-licensed vaccines.

When IXIARO is administered concomitantly with injectable vaccines, they should be given with separate syringes at different injection sites. IXIARO should not be mixed with any other vaccine in the same syringe or vial.

7.2 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

Pregnancy category B. Reproduction studies have been performed in female rats at doses approximately 300-fold excess relative to the projected human dose (on a mg/kg basis) and have revealed no evidence of impaired fertility or harm to the fetus due to IXIARO.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, IXIARO should be used during pregnancy only if clearly needed.

The effect of IXIARO vaccine on embryofetal and pre-weaning development was evaluated in a developmental toxicity study using pregnant rats. One group of rats was administered IXIARO twice prior to gestation and once during the period of organogenesis (gestation Day 6). A second group of pregnant rats was administered IXIARO once prior to gestation and once during the period of organogenesis (gestation Day 6). IXIARO was administered at 0.5 mL/rat/occasion (approximately 300-fold excess relative to the projected human dose on a mg/kg basis), by intramuscular injection. No adverse effects on mating, fertility, pregnancy, parturition, lactation, embryofetal or pre-weaning development were observed. There was a statistically significant finding of incomplete ossification in a few fetuses derived from the second group of pregnant rats. However, there are no data to suggest that this finding is vaccine related. There were no vaccine-related fetal malformations or other evidence of teratogenesis noted in this study.

8.3 Nursing Mothers

It is not known whether IXIARO is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if IXIARO is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of IXIARO have not been established in infants younger than 2 months of age [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, no subjects who received JE-VAX, and one subject (5.9%) who received 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]. The SAEs occurring in the IXIARO group were as follows: one case each of rectal hemorrhage, pancreatic adenocarcinoma, breast cancer, and one death in a subject with metastatic lung adenocarcinoma, which occurred four months after the subject completed the two-dose regimen.

11 DESCRIPTION

IXIARO, Japanese Encephalitis Vaccine, Inactivated, Adsorbed is a sterile suspension for intramuscular injection. Each 0.5 mL dose of vaccine contains approximately 6 mcg of purified, inactivated JE proteins and 250 mcg of aluminum hydroxide. The appearance of the liquid is a white, opaque, non-uniform suspension which becomes homogenous upon shaking.

IXIARO is a vaccine prepared by propagating JEV strain SA14-14-2 in vero cells. Multiple viral harvests are pooled, clarified and concentrated. The virus suspension is treated with propanol 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 protein concentration 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

| Table 6. Rates of Solicited Adverse Reactions on Days 0-7 After Each IXIARO 0.5 mL Vaccination in Children 3 Years to <18 Years of Age Traveling From Western Countries, Study 2† |
|------------------------------------------|----------------|----------------|----------------|
|                                         | Post Dose 1 (N=556) | Post Dose 2 (N=499) |
| Injection Site Reactions | % of subjects | % of subjects | % of subjects |
| Pain | 18.2 | 16.3 | 18.2 |
| Itching | 3.6 | 2.0 | 3.6 |
| Tenderness | 30.9 | 24.5 | 30.9 |
| Hardening | 0.0 | 2.0 | 0.0 |
| Swelling | 0.0 | 0.0 | 0.0 |
| Redness | 5.5 | 0.0 | 5.5 |

| Solicited Systemic Reaction | % of subjects | % of subjects | % of subjects |
| Irritability | 0.0 | 6.1 | 0.0 |
| Nausea | 1.8 | 2.0 | 1.8 |
| Vomiting | 0.0 | 2.0 | 0.0 |
| Diarrhea | 1.8 | 0.0 | 1.8 |
| Flu-like symptoms | 0.0 | 0.0 | 0.0 |
| Excessive fatigue | 12.7 | 0.0 | 12.7 |
| Muscle pain | 27.3 | 2.0 | 27.3 |
| Rash | 1.8 | 2.0 | 1.8 |
| Headache | 1.8 | 4.1 | 1.8 |
| Loss of appetite | 1.8 | 0.0 | 1.8 |
| Fever ≤37.7°C (≥99.9°F) | 5.5 | 2.0 | 5.5 |
| 37.8-38.6 °C (99.9-101.5°F) | 3.6 | 2.0 | 3.6 |
| 38.7-39.3 °C (101.6-102.7°F) | 1.8 | 0.0 | 1.8 |
| 39.4-40.5 °C (102.8-104.9°F) | 0.0 | 0.0 | 0.0 |
| >40.5°C (>104.9°F) | 0.0 | 0.0 | 0.0 |

7.6 Data

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

| Table 7. Rates of Common Solicited and Unsolicited Systemic Adverse Events* in Adults Residing in Non-Endemic Areas After IXIARO or Control [PBS + Al(OH)₃], Safety Population, Study 4§ |
|------------------------------------------|----------------|----------------|----------------|
|                                         | Post Dose 1 (Day 0 to Day 28) | Post Dose 2 (Day 28 to Day 56) | Post Dose 1 or Dose 2 (Day 0 to Day 56) |
| Adverse Event | % of subjects | % of subjects | % of subjects |
| Headache† | 21.6 | 20.2 | 21.6 |
| Myalgia† | 13.3 | 12.9 | 13.3 |
| Fatigue† | 8.6 | 8.7 | 8.6 |
| Influenza-like Illness† | 8.2 | 8.5 | 8.2 |
| Nausea† | 4.7 | 5.3 | 4.7 |
| Nasopharyngitis | 2.3 | 1.8 | 2.3 |
| Fever† | 1.9 | 2.1 | 1.9 |
| Rhinitis | 1.0 | 0.8 | 1.0 |
| Upper Respiratory Tract Infection | 0.9 | 0.9 | 0.9 |
| Back Pain | 0.8 | 0.9 | 0.8 |
| Pharyngolaryngeal Pain | 0.8 | 0.9 | 0.8 |
| Rash† | 0.8 | 0.9 | 0.8 |
| Diarrhea | 0.8 | 0.8 | 0.8 |
| Cough† | 0.8 | 0.8 | 0.8 |
| Fatigue† | 0.6 | 0.8 | 0.6 |

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

§NCT00477978

n=number of subjects with available diary card data for each dose, used as the denominator to calculate percentages.
more than 200 ppm), bovine serum albumin (not more than 100 ng/mL), host cell DNA (not more than 200 pg/mL), sodium metabolabisulfite (not more than 200 ppm), host cell protein (not more than 100 ng/mL), and proteamine 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 (PRNT50) with a threshold titer of ≥1:10, provides evidence of protective immunity. The evaluation of vaccine effectiveness of IXIARO was therefore based on neutralizing antibody response using a threshold PRNT50 titer of ≥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 maintained intramuscularly with doses of up to 300-fold excess relative to the projected human dose (on a mg/kg basis) administered prior to and after mating (See Use in Specific Populations (8.1)). The effect of IXIARO on male fertility has not been evaluated.

14 CLINICAL STUDIES
Immunogenicity of IXIARO in a Pediatric Clinical Trial in the Philippines
The immunogenicity of IXIARO was evaluated in a randomized, double-blind, controlled, open-label clinical trial in healthy children conducted in the Philippines (Study 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 Prevar (Pneumococcal 7-valent Conjugate Vaccine (Pneumovax 7-p). Subjects in the IXIARO treatment arm received intramuscular doses on Day 0 and Day 28. A total of 396 subjects from the group administered IXIARO (0.25 mL for infants and 0.5 mL for children 2 months to <3 years of age and 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 PRNT50 titer ≥1:10. The 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 displayed in Table 9.

Immunogenicity of IXIARO in a Pediatric Clinical Study in Children 2 Months to <18 Years of Age Traveling from Non-Endemic Countries
The immunogenicity of IXIARO was evaluated in an uncontrolled, open-label clinical study conducted in the United States, Europe and Australia in healthy male and female children with planned travel to JEV-endemic areas (Study 2)1. 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. An analysis was carried out on immunogenicity data for the first 54 subjects enrolled (median age: 15.2 years, range 10 months to 17 years; 59.3% female; ethnicity: 81.5% Asian, 14.8% Black, 3.7%). (See Adverse Reactions (6.1)).

JEV neutralizing antibody titers were available for 51 subjects at Day 56. The proportion of those subjects with PRNT50 titer ≥1:10 was 60% (31/51). GMT was 72.2 (95% CI 38.0, 144.6) at Day 56 and 78.2 (95% CI 41.4, 140.5) at Month 7. The proportion of subjects with PRNT50 titers ≥1:10 at Day 56 and Month 7, and GMTs were 18.0 (95% CI 9.3, 31.3) and 78.2 (95% CI 34.6, 160.5), respectively.

Persistence of Neutralizing Antibody Response in Adults
The persistence of IXIARO in a clinical trial conducted in the U.S., Germany and Austria (Study 3)2 in 867 healthy adults 18 years of age and older (median age: 41 years; 50.8% female; ethnicity: 80% Caucasian, 10.3% Asian, 8.8% 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 buffer 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 PRNT50 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 PRNT50 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 (PRNT50 titer <1:10).

Table 8. Rates of Injection Site Adverse Reactions* After IXIARO or Control (PBS + Al(OH)3), Adults Residing in Non-Endemic Areas, Safety Population With Evaluable Diary Cards, Study 4

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Proportion of Subjects with PRNT50 titer ≥1:10 (n/N) [95% CI]</th>
<th>n/N</th>
<th>[95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Vaccination</td>
<td>30% (3/10) [9.8, 49.8]</td>
<td>10/30</td>
<td>0% (0/0) [95% CI 0.0, 14.3]</td>
</tr>
<tr>
<td>Day 56</td>
<td>100% (9/9) [99.2, 100.0]</td>
<td>9/9</td>
<td>100% (1/1) [90.9, 100.0]</td>
</tr>
<tr>
<td>Day 56</td>
<td>100% (10/10) [95.4, 100.0]</td>
<td>10/10</td>
<td>100% (1/1) [90.9, 100.0]</td>
</tr>
</tbody>
</table>

Table 9. JEV-Neutralizing Antibody Response After IXIARO* Among Children 2 Months to <18 Years of Age Residing in the Philippines, Intent-To-Treat Population**, Study 1

<table>
<thead>
<tr>
<th>Age Group</th>
<th>2 months – &lt;6 months</th>
<th>6 months – &lt;12 months</th>
<th>1 year – &lt;3 years</th>
<th>3 years – &lt;12 years</th>
<th>12 years – 18 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Point</td>
<td>Proportion of Subjects with PRNT50 titer ≥1:10 (n/N) [95% CI]</td>
<td>n/N</td>
<td>[95% CI]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Vaccination</td>
<td>2.6 (11/420) [95% CI 1.9, 3.4]</td>
<td>420</td>
<td>0.0 (0/0) [95% CI 0.0, 0.0]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 56</td>
<td>100% (72.2, 100.0) [95% CI 72.2, 100.0]</td>
<td>100</td>
<td>100% (78.2, 90.6) [95% CI 78.2, 90.6]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 56</td>
<td>100% (100.0, 100.0) [95% CI 100.0, 100.0]</td>
<td>100</td>
<td>100% (96.3, 100.0) [95% CI 96.3, 100.0]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 10. All subjects were seronegative at baseline (PRNT50 titer <1:10).
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 Titer ≥1:10 was 100% (95% CI: 87.5, 100.0), and the GMT was 253.67 [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 7). Subjects were divided into three treatment groups: Group A (N=62) received IXIARO (Day 0 and 28) + HAVRIX (Day 0); Group B (N=65) received IXIARO (Day 0 and 26) + control (0.5 mL phosphate buffered saline with 0.1% aluminum hydroxide by intramuscular injection on Day 0); and 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).

**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). Four weeks after this delayed second dose, 99.0% of subjects (99/100) had a PRNT Titer ≥1:10 (GMT 504.3 [95% CI: 367.3, 692.3]). One year later, 88.5% of subjects (88/100) had a PRNT Titer ≥1:10 (99/100) had anti-HAV GMT at Day 28 after vaccine dose 1, 99.0% of subjects (99/100) had anti-JEV GMT at Day 56 after vaccine dose 2.

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**Table 10. JEV-Neutralizing Antibody Response After IXIARO or JE-VAX Among Adults Residing in Non-Endemic Areas, Per Protocol Population*, Study 4**

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Proportion of Subjects with PRNT Titer ≥1:10 (n/N) [95% CI]</th>
<th>Geometric Mean Titers◊ [N] [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 28 (28 days after vaccine dose 2)</td>
<td>IXIARO (n=361) [95% CI] 98.5% (95%, 99.5%)</td>
<td>JE-VAX (N=364) [95% CI] 98.5% (95%, 99.5%)</td>
</tr>
<tr>
<td>Day 56 (28 days after vaccine dose 2)</td>
<td>98.5% (191/194) [95%, 99.5%]</td>
<td>99.5% (194/195) [95%, 99.5%]</td>
</tr>
</tbody>
</table>

**Table 11. JEV-Neutralizing Antibody Response During the Vaccination Series (IXIARO on Days 0 and 28) Among Adults Residing in Non-Endemic Areas, Per Protocol Population*, Study 6**

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Proportion of Subjects with PRNT Titer ≥1:10 (n/N) [95% CI]</th>
<th>Geometric Mean Titers◊ [N] [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 28 (28 days after vaccine dose 1)</td>
<td>IXIARO (n=224) [95% CI] 98.1% (95%, 100.0%)</td>
<td>JE-VAX (N=226) [95% CI] 98.1% (95%, 100.0%)</td>
</tr>
</tbody>
</table>

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**Table 12. JEV-Neutralizing Antibody Response Following a Booster Dose of IXIARO Administered 14 Months After Completion of the Primary Series Among Adults Residing in Non-Endemic Areas, Intent to Treat Population*, Study 5**

<table>
<thead>
<tr>
<th>Time Point</th>
<th>% PRNT Titer ≥1:10 (n/N) [95% CI]</th>
<th>Geometric Mean Titers◊ [N] [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-booster, Day 0</td>
<td>IXIARO (n=179) [95% CI] 69.2% (62.4%, 75.2%)</td>
<td>JE-VAX (N=181) [95% CI] 22.5% (19.0, 26.7)</td>
</tr>
<tr>
<td>Day 28</td>
<td>101.0% (n=198) [98%, 100.0%]</td>
<td>98.5% (194/195) [95.6%, 99.5%]</td>
</tr>
<tr>
<td>Day 12</td>
<td>98.5% (191/194) [95.6%, 99.5%]</td>
<td>361.4 (194) [294.5, 443.5]</td>
</tr>
</tbody>
</table>

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16.1 How Supplied

IXIARO is supplied as a sterile 0.5 mL solution in a pre-filled syringe (Type 1 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 62515-001-01. 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. 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 heart beat, hives).
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 (JEV). 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.
  - have 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. Ideally, the doses are given as:

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

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 components of 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.