

## 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

#### INDICATIONS AND USAGE

- IXIARO is a vaccine indicated for active immunization for the prevention of disease caused by Japanese encephalitis virus (JEV) in persons 17 years of age and older. (1)

#### DOSAGE AND ADMINISTRATION

- Primary immunization consists of 2 doses administered 28 days apart. (2)
- Each 0.5 mL dose is administered intramuscularly. (2)
- Immunization series should be completed at least 1 week prior to potential exposure to JEV. (2, 14)

- If the primary series was administered more than 1 year previously, a booster dose may be given prior to potential re-exposure. (2, 1)

#### DOSAGE FORMS AND STRENGTHS

- Suspension for injection supplied in 0.5 mL single dose syringes. (3, 11)

#### CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of IXIARO is a contraindication to administration of IXIARO. (11)

#### WARNINGS AND PRECAUTIONS

- IXIARO contains protamine sulfate, a compound known to cause hypersensitivity reactions in some individuals. (5, 11)

#### ADVERSE REACTIONS

- The most common ( $\geq 10\%$ ) systemic adverse events were headache and myalgia. The most common ( $\geq 10\%$ ) injection-site reactions were pain and tenderness (6)

To report SUSPECTED ADVERSE REACTIONS, contact InterCell USA, Inc. at 1-240-454-7333 or VAERS at 1-800-822-7967 or [www.vaers.hhs.gov](http://www.vaers.hhs.gov).

#### USE IN SPECIFIC POPULATIONS

Safety and effectiveness have not been established in pregnant women, nursing mothers, or in children and adolescents (younger than 17 years of age). (8.1, 8.2, 8.3)

To report INADVERTANT USE IN PREGNANT WOMEN, contact InterCell USA, Inc. at 1-240-454-7333.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.  
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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

IXIARO is a vaccine indicated for the prevention of disease caused by Japanese encephalitis virus (JEV) in persons 17 years of age and older.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Immunization Series

Primary immunization with IXIARO consists of 2 doses administered 28 days apart. Immunization series should be completed at least 1 week prior to potential exposure to JEV.

If the primary series was administered more than 1 year previously, a booster dose may be given prior to potential re-exposure. Data on the timing of, and the response to, a booster administered more than 2 years after receipt of the final dose of vaccine (primary series or booster) are not available.

#### 2.2 Administration

Before administration, shake the syringe well to obtain a white, opaque, homogeneous suspension. Do not administer if particulate matter remains following shaking or if discoloration is observed. Each 0.5 mL dose of IXIARO is administered intramuscularly into the deltoid

muscle. Do not administer intravenously, intradermally, or subcutaneously.

### 3 DOSAGE FORMS AND STRENGTHS

IXIARO is a suspension for injection supplied in 0.5 mL single dose syringes. [See Description (11)].

### 4 CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of IXIARO is a contraindication to administration of IXIARO [See Description (11)].

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Preventing and Managing Allergic Vaccine 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 Limitations of Vaccine Effectiveness

Vaccinees who receive only one dose of IXIARO may have a suboptimal response and may therefore incur higher risk if exposed to JEV compared to vaccinees who receive both doses. Vaccination with IXIARO may not result in protection in all cases. IXIARO will not protect against encephalitis caused by viruses/pathogens other than JEV.

#### 5.3 Altered Immunocompetence

There are no safety or efficacy data regarding the use of IXIARO in immunocompromised individuals. Immunocompromised individuals may have a diminished immune response to IXIARO.

### 6 ADVERSE REACTIONS

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.

#### 6.1 Clinical Trials Experience

The most common ( $\geq 10\%$ ) systemic adverse events observed in clinical trials with IXIARO were headache and myalgia. The most common ( $\geq 10\%$ ) local reactions after IXIARO administration were pain and tenderness.

In seven randomized, controlled clinical studies and one uncontrolled clinical study<sup>1,2,3,4,5,6,7,8</sup> conducted in North America, Europe, Australia and New Zealand, a total of 3,945 healthy adults aged 18 to 86 years received at least one dose of IXIARO, of which 3,558 were followed-up for safety for 6 to 36 months after the first dose and further 387 were followed-up for safety for two months. 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 1.8% of subjects who received IXIARO experienced a serious adverse event, including one case of multiple sclerosis. Approximately 1% of subjects who received IXIARO discontinued due to adverse events.

#### Adverse Events in a Clinical Trial Comparing IXIARO to a Control:

The safety of IXIARO was evaluated in a randomized, controlled, double-blind clinical trial in healthy male and female subjects<sup>1</sup>. IXIARO was compared to a control: Phosphate Buffered Saline containing 0.1% aluminum hydroxide [PBS + Al(OH)<sub>3</sub>]. 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)<sub>3</sub> (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)<sub>3</sub> (mean age: 33.8 years, range 18 to 86 years; 55.3% female; race: 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.

#### 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)<sub>3</sub> 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)<sub>3</sub> group. The severity of adverse events was as follows: mild in 33.7% of subjects receiving IXIARO compared to 34.1% of subjects receiving PBS + Al(OH)<sub>3</sub>, moderate in 20.1% of subjects receiving IXIARO compared to 17.4% of subjects receiving PBS + Al(OH)<sub>3</sub>, and severe in 5.1% of subjects receiving IXIARO compared to 5.2% of subjects receiving PBS + Al(OH)<sub>3</sub>. Severity was defined as follows: Mild, awareness of signs or symptoms, but easily tolerated; Moderate, discomfort enough to interfere with usual activity; and Severe, incapable of work or usual activity. Adverse events of any severity grade occurring with an incidence of ≥1% of subjects are shown in Table 1.

#### Injection Site Reactions

Injection site reactions after IXIARO were compared to reactions after PBS + Al(OH)<sub>3</sub>. 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. Pain, tenderness, and pruritis severity was assessed subjectively as absent, mild, moderate or severe by the subject. The amount of erythema, induration and edema was measured by the subject and/or the investigator and rated as absent, mild (≤1cm), moderate (>1 to <3cm), or severe (≥3cm). The severity of injection site reactions observed after either dose was as follows: mild in 41.6% of subjects receiving IXIARO compared to 44.2% of subjects receiving PBS + Al(OH)<sub>3</sub>, moderate in 9.5% of subjects receiving IXIARO compared to 7.7% of subjects receiving PBS + Al(OH)<sub>3</sub>, and severe in 3.2% of subjects receiving IXIARO compared to 3.1% of subjects receiving PBS + Al(OH)<sub>3</sub>. The frequency of injection site reactions of any severity grade is shown in Table 2.

#### Adverse Events in a Clinical Trial Comparing IXIARO to JE-VAX:

The safety of IXIARO compared to another inactivated JE vaccine (JE-VAX) was evaluated in a randomized, double-blind clinical trial<sup>2</sup>.

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 2<sup>nd</sup> dose of IXIARO. The most common adverse events after immunization occurring in ≥1% of subjects were headache, myalgia, fatigue, influenza-like illness, nausea, nasopharyngitis, pyrexia, 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 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:

The safety of a IXIARO booster dose administered 15 months after the first dose of the primary series was evaluated in an open-label, uncontrolled trial<sup>3</sup>. 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 vaccina-

tion. 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). Pain and tenderness were the most common injection site reactions (>10% of subjects); nasopharyngitis and headache were the most common systemic adverse events (>10%).

#### Safety in Concomitant Use with the Hepatitis A Vaccine, HAVRIX<sup>4</sup>

The safety of IXIARO when administered concomitantly with inactivated Hepatitis A Virus vaccine (HAVRIX) was evaluated in a controlled trial in which subjects 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)<sub>3</sub>]; Group C (N=65) received HAVRIX + control [PBS + Al(OH)<sub>3</sub>]. 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 2<sup>nd</sup> 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 events have been reported during post-marketing use of IXIARO. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate 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<sup>4</sup>, 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

**Table 1. Common Systemic Adverse Events\* After IXIARO or Control [PBS + Al(OH)<sub>3</sub>], Safety Population**

Adverse Event	Incidence (% of subjects) in the First Vaccination Period (Day 0 to Day 28)		Incidence (% of subjects) in the Second Vaccination Period (Day 28 to Day 56)		Incidence (% of subjects) in the Total Vaccination Period (Day 0 to Day 56)	
	IXIARO	PBS + Al(OH) <sub>3</sub>	IXIARO	PBS + Al(OH) <sub>3</sub>	IXIARO	PBS + Al(OH) <sub>3</sub>
	N# = 1993	N# = 657	N# = 1968	N# = 645	N# = 1993	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
Pyrexia†	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

\* The adverse events in this table are those observed at an incidence of ≥ 1% in the IXIARO or PBS + Al(OH)<sub>3</sub> groups.

† These symptoms were solicited in a subject diary card. Percentages 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

**Table 2. Injection Site Solicited Adverse Reactions\* After IXIARO or Control [PBS + Al(OH)<sub>3</sub>], Subjects in the Safety Population With Evaluable Diary Cards**

Adverse Reaction	Incidence Post Dose 1 (% of subjects)†		Incidence Post Dose 2 (% of subjects)†		Incidence Post Dose 1 or Dose 2 (% of subjects)†	
	IXIARO	PBS + Al(OH) <sub>3</sub>	IXIARO	PBS + Al(OH) <sub>3</sub>	IXIARO	PBS + Al(OH) <sub>3</sub>
	N# = 1963	N# = 645	N# = 1951	N# = 638	N# = 1963	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
Pruritis	2.6	3.3	1.6	1.9	3.8	4.5

\* 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

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

There are no data regarding the use of IXIARO concomitantly with immunosuppressive therapies, e.g., irradiation, anti-metabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses) [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 embryo-fetal 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, embryo-fetal 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.

### 8.2 Nursing Mothers

It is not known whether this vaccine 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.

### 8.3 Pediatric Use

Safety and effectiveness of IXIARO in a pediatric population (<17 years of age) has not been established.

### 8.4 Geriatric Use

Clinical studies of IXIARO did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. The limited dataset from the pivotal efficacy study<sup>2</sup> is as follows: in

**Table 3. Seroconversion Rates and Geometric Mean Titers After IXIARO or JE-VAX, Per Protocol Population**

Time Point	Seroconversion Rates		Rate difference [95% CI]
	IXIARO SCR (n/N) [95% CI]	JE-VAX SCR (n/N) [95% CI]	
Pre-Vaccination Screen	0	0	
Day 56 (28 days after vaccine dose #2)	<b>96.4%</b> (352/365) [94.0, 97.9]	<b>93.8%</b> (347/370) [90.9, 95.8]	<b>2.6%</b> [-0.5, 6.0]†
Time Point	Geometric Mean Titers		GMT ratio estimator [95% CI]
	IXIARO N=365 n (GMT) [95% CI's]	JE-VAX N=370 n (GMT) [95% CI's]	
Pre-Vaccination Screen	365 ( <b>5.0</b> ) $\diamond$	370 ( <b>5.0</b> ) $\diamond$	
Day 56 (28 days after vaccine dose #2)	361 ( <b>243.6</b> ) [216.4, 274.1]	364 ( <b>102.0</b> ) [90.3, 115.2]	2.33 [1.97, 2.75]‡

† Seroconversion Rates (SCRs): Non-inferiority of IXIARO compared to JE-VAX for SCR was demonstrated if the lower bound of the 2-sided 95% confidence interval (CI) for the SCR difference (IXIARO minus JE-VAX) was > -10% at Day 56.

‡ Geometric Mean Titers (GMTs): Non-inferiority of IXIARO compared to JE-VAX for GMTs 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.

$\diamond$  Pre-Vaccination titers were negative by definition in the PP population and have been imputed to 5.

**Table 4. SCR and GMT Before and at Months 1, 6 and 12 After a Booster Dose Administered to Subjects at 15 Months After Primary Immunization with IXIARO (ITT population)**

Time Point	SCR (n/N)	Geometric Mean Titers
	[95% CI]	GMT (n) [95% CI's]
Pre-booster, Day 0	<b>69.2%</b> (137/198) [62.4%, 75.2%]	<b>22.5</b> (198) [19.0, 26.7]
Day 28	<b>100.0%</b> (198/198) [98.1%, 100.0%]	<b>900.1</b> (198) [742.4, 1091.3]
Month 6	<b>98.5%</b> (194/197) [95.6%, 99.5%]	<b>487.4</b> (197) [390.7, 608.1]
Month 12	<b>98.5%</b> (191/194) [95.6%, 99.5%]	<b>361.4</b> (194) [294.5, 443.5]

**Table 5. Seroconversion Rates (SCR) During the Vaccination Series (IXIARO on Days 0 and 28), Per Protocol Population**

Day 0 (Dose #1 administered)	Day 10 (10 days post dose #1)	Day 28 (28 days post dose #1)	Day 28 (Dose #2 administered)	Day 35 (7 days post dose #2)	Day 56 (28 days post dose #2)
	SCR (n/N) [95% CI]	SCR (n/N) [95% CI]		SCR (n/N) [95% CI]	SCR (n/N) [95% CI]
	<b>21.1%</b> (24/114) [13.6%; 28.5%]	<b>39.8%</b> (45/113) [30.8%; 48.8%]		<b>97.3%</b> (110/113) [94.4%; 100.0%]	<b>97.3%</b> (110/113) [94.4%, 100%]

subjects  $\geq 65$  years of age who received IXIARO per protocol (N=24), seroconversion rate was 95.8% and geometric mean titer was 255.2.

In subjects  $\geq 65$  years of age who had been vaccinated in any of five trials<sup>1, 2, 4, 5</sup> 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)<sub>3</sub>] group. Five serious adverse events (SAE) were reported. 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)<sub>3</sub>] experienced a SAE. The serious adverse events 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 dose of vaccine contains approximately 6 mcg of purified, inactivated JEV proteins and 250 mcg of aluminum hydroxide. The appearance of the liquid is a white, opaque, non-uniform suspension which

becomes homogeneous upon shaking. As IXIARO is inactivated, it cannot cause Japanese Encephalitis.

IXIARO is a vaccine prepared by propagating JEV strain SA<sub>14-14-2</sub> in Vero cells. Multiple viral harvests are performed, which 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 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 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 proteins (not more than 300 ng/6 $\mu$ g of protein), and protamine sulfate (not more than 1 $\mu$ g/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.

## 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 at intramuscular 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

Clinical efficacy trials of JE vaccines have found that neutralizing antibody, as measured by a Plaque Reduction Neutralization Test (PRNT) is protective against JEV infection<sup>9</sup>. Therefore, the evaluation of the efficacy of IXIARO was based on immunogenicity using PRNT as a serological correlate of protection. The World Health Organization consultation group recognizes a PRNT titer of  $\geq 1:10$  as being a reasonable correlate for protection<sup>10</sup>.

### Clinical Trial<sup>2</sup> of Immunogenicity of IXIARO – Non-inferiority of IXIARO Compared to U.S.-Licensed JE Vaccine, JE-VAX

Immunogenicity of the vaccine was evaluated in a randomized, active-controlled, observer-blinded clinical trial conducted in the U.S., Germany and Austria in 867 healthy male and female subjects 18 to 80 years of age (mean age: 41.3 years; 60.8% female; race: 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, 0.5 mL of IXIARO, Day 7, PBS + Al(OH)<sub>3</sub> (0.5 mL phosphate buffered saline with 0.1% aluminum hydroxide), and on Day 28, 0.5 mL of 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.

The co-primary endpoints were seroconversion rate (SCR), defined as anti-JEV antibody titer  $\geq 1:10$ , and geometric mean titer (GMT) at Day 56 in the per protocol population. The immune responses elicited by IXIARO met predefined statistical criteria for non-inferiority compared to those induced by JE-VAX. See Table 3.

### Follow-up Study of Long Term Immunogenicity (6, 12, 24 and 36 months)

The persistence of JE-neutralizing antibody was evaluated in a subgroup of subjects recruited for follow-up after participation in one of two clinical trials<sup>1, 2</sup>. In the Intent-to-Treat (ITT) population of subjects randomized to vaccination with IXIARO (N=181) and in the ITT36 population of subjects who intended to stay in the study until month 36 (N = 152), seroconversion rates (SCR) at 6; 12; 24 and 36 months after initiation of the two-dose series were 95% [95%CI 90.8,97.4] and 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] and 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.

### Clinical Trial<sup>3</sup> on the Effect of a Booster Dose of IXIARO on Long-term Immunity

A single 6 mcg booster dose of IXIARO was evaluated in 198 subjects in an uncontrolled, open-label phase 3 study at 15 months after the first IXIARO injection.

At 1 month after the booster, GMT was 900.1 (a 40-fold increase from day 0 prior to the booster vaccination) and a SCR of 100% was observed. At 12 months after the booster, a GMT of 361.4 and a SCR of 98.5% (primary endpoint) were observed. The immune response (SCR and GMT) following a booster dose of IXIARO at various time points is summarized below. See Table 4.

### Temporal Evaluation of Immunogenicity of IXIARO During Vaccination Series

In a randomized, dosing regimen, observer-blinded clinical trial<sup>4</sup> in 374 healthy male and female subjects, aged 18-76 years, the immunogenicity of IXIARO was evaluated on days 10, 28, 35, and 56 during the vaccination period. Seroconversion rates (SCR) at each time point for the subjects randomized to the standard dosing regimen (IXIARO on days 0 and 28) are displayed in Table 5.

### Immunogenicity of IXIARO Booster Doses

The immunogenicity of booster doses was assessed in seronegative subjects in a study<sup>7</sup> investigating persistence of immunity following three different primary immunization regimens (2x6 mcg, 1x12mcg or 1x6 mcg). Booster doses were administered at 11 or 23 months after the first dose to subjects with JE-neutralizing antibody titers < 1:10.

Results showed that the second injection can be given up to 11 months after the first one. When a second dose was given 11 months after the first dose, seroconversion rate was 99.0% (99/100) with a GMT of 504.3 [95% CI: 367.3, 692.3] four weeks after vaccination, and by Month 24 was 88.5% (85/96; GMT 121.0 [95% CI: 87.4, 167.6]) without any further booster. In the group with two-dose primary immunization, the rates of subjects with persistent JE-neutralizing antibody titers  $\geq 1:10$  without a booster at months 12 and 24 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]. After administration of a booster dose to subjects with JE-neutralizing antibody titers < 1:10 in the group with complete primary immunization, SCRs 4 weeks after the booster at months 11 and 23 were 100% [17/17, 95% CI 81.6,100.0] and 100% [27/27, 95% CI 87.5,100.0] respectively, and GMTs were 673.6 [95% CI 378.7,1198.2], and 2536.7 [95% CI 1467.7,4384.4], respectively.

### Clinical Trial<sup>4</sup> of Immunogenicity of IXIARO and the Hepatitis A Vaccine, HAVRIX, When Used Concomitantly

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 male and female subjects aged 18 to 61 years. Subjects were divided into three treatment groups: Group A (N=62) received IXIARO + HAVRIX; Group B (N=65) received IXIARO + control [PBS + Al(OH)<sub>3</sub>] (0.5mL phosphate buffered saline with 0.1% aluminum hydroxide by intramuscular injection); Group C (N=65) received HAVRIX + control [PBS + Al(OH)<sub>3</sub>]. 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 Section 6.2, Clinical Trials Experience.

### 15 REFERENCES

1. Clinical study referred to as NCT00605085 in the National Library of Medicine clinical trial database, also referred to as study IC51-302 in the Biologics License Application.
2. 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.

3. 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.
4. Clinical study referred to as NCT00596271 in the National Library of Medicine clinical trial database, also referred to as study IC51-308 in the Biologics License Application.
5. Clinical study 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.
6. 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.
7. Clinical study 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.
8. Clinical study referred to as NCT00595465 in the National Library of Medicine clinical trial database, also referred to as study IC51-310 in the Biologics License Application
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.

### 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 2 syringes with or without separate needles. NDC 42515-001-02. None of the syringe or packaging materials contain latex.

#### 16.2 Storage Conditions

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.

#### 16.3 Handling

Prior to agitation, IXIARO may appear as a clear liquid with a white precipitate. After thorough agitation, it forms a white, cloudy liquid/suspension. The vaccine should be visually inspected for coarse particulate matter and discoloration prior to administration. Discard the product if particulates are present or if it appears discolored or if the syringe appears to be physically damaged. To attach Luer

needle, 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.**

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

### 17 PATIENT COUNSELING INFORMATION

#### 17.1 Counseling by the Health Care Provider

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

Current U.S. and international advisories should be consulted regarding prevalence of Japanese encephalitis in specific locations. Counsel persons traveling to epidemic and endemic areas 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). When educating vaccine recipients regarding the potential side effects, explain that IXIARO contains formalin-inactivated JEV particles and is, therefore, non-infectious. Give the required vaccination information to the vaccine recipient, and provide an opportunity to discuss any questions or concerns. Instruct the vaccine recipient to report any adverse reactions to their health care provider.

#### 17.2 FDA-Approved Patient Labeling

Manufactured by:  
Intercell Biomedical Ltd.  
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F: +44.1506.446.601  
www.intercell.com

Distributed by:  
Intercell USA, Inc.  
22 Fairfield Road  
Gaithersburg, MD 20878  
USA



## Patient Information about IXIARO (pronounced "ik-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 persons 17 years 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.

IXIARO is not approved for use in children.

#### 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.
- 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. 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.

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 maximum protection may not be achieved 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 are headache, muscle pain and injection site reactions (e.g., pain, swelling, tenderness, redness). Nausea, skin rash, fatigue, flu-like illness, and fever may also occur. 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.

#### 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](http://cdc.gov) and [who.int](http://who.int)) also provide additional information about JEV and related travel advisories.

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#### License Holder:

Intercell AG, Vienna, Austria

#### Manufacturer:

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