PRODUCT MONOGRAPH

IXIARO*

Japanese encephalitis vaccine (inactivated, adsorbed)

Suspension for injection

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

Manufactured for:
Novartis Pharmaceuticals Canada Inc.
385 Bouchard Blvd.
Dorval, Quebec H9S 1A9

Date of Revision:

Date of Approval:
October 8, 2013

Submission Control No: 168092

Table of Contents

IXIARO*

Japanese encephalitis vaccine (inactivated, adsorbed)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Pharmacotherapeutic group: Encephalitis vaccines.
ATC code: J07BA02

Table 1: Summary Product Information

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular	0.5 mL suspension for injection containing 6 mcg Protein and having a potency ≤ 460 ng ED_{50}	Adjuvant: Aluminium hydroxide Phosphate Buffered Saline: Sodium chloride, Potassium dihydrogen phosphate, Disodium hydrogen phosphate, Water for injection *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

IXIARO* Japanese Encephalitis Virus, purified inactivated vaccine is a sterile, ready to use suspension for intramuscular use.
The vaccine is prepared by propagating Japanese encephalitis virus strain (SA_{14}-14-2) in Vero cells. The virus suspension is treated with protamine sulphate to remove contaminating DNA and proteins. The purified virus is then inactivated by treatment with formaldehyde, adjusted to a specified protein concentration and formulated by addition of aluminium hydroxide adjuvant. No preservatives or antibiotics are added to the formulation.

Each dose of vaccine contains 6 micrograms (mcg) of purified, inactivated JE virus preparation and 0.1% aluminium hydroxide, hydrated corresponding to 0.25 mg Al/dose. The potency of the vaccine is measured as minimum amount of vaccine required to seroconvert 50 % of mice.

INDICATIONS AND CLINICAL USE

IXIARO* is indicated for active immunization against Japanese encephalitis for persons 18 years of age and older.
IXIARO* should be considered for use in individuals at risk of exposure through travel or in

the course of their occupation.

CONTRAINDICATIONS

- Patients who are hypersensitive to this vaccine or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Individuals who show hypersensitivity reactions after receiving the first dose of the vaccine should not be given the second dose.
- As with other vaccines, vaccination with IXIARO* must be postponed in persons with acute severe febrile conditions.

WARNINGS AND PRECAUTIONS

As with any other vaccine, vaccination with IXIARO* may not result in protection in all cases.
IXIARO* will not protect against encephalitis caused by other micro-organisms.

Serious Warnings and Precautions

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

- IXIARO* should under no circumstances be administered intravascularly.
- Like other intramuscular injections, this vaccine should not be administered intramuscularly to persons with thrombocytopenia, haemophilia or other bleeding disorders.

Special Populations

Pregnant Women:
There are limited amount of data from the use of IXIARO* in pregnant women. In animal studies findings of unclear clinical relevance have been identified .
As a precautionary measure, the use of IXIARO* during pregnancy or lactation should be avoided.

Nursing Women:
IXIARO* should be given to a nursing woman only if the benefit outweighs the theoretical risks to mother and child.
It is unknown whether IXIARO* is excreted in human milk.
No effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to IXIARO* is negligible.

Pediatrics (< 18 years of age):
IXIARO* is not recommended for use in persons below 18 years of age due to a lack of data on safety and efficacy in this population.

Geriatrics (≥ 65 years of age):
Special studies in the geriatric population were not performed; however, IXIARO* has been administered to 120 subjects ≥65 years of age. No overall differences in safety and efficacy were observed between these subjects.

Immunosuppressed Individuals:
In patients receiving immunosuppressive therapy or patients with immunodeficiency an adequate immune response may be diminished.

Monitoring and Laboratory Tests
Not applicable.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse drug reactions reported after use of IXIARO* include dyspnoea, neuritis, and thrombocytopenia. The most frequently reported adverse drug reactions are fatigue, headache, influenza like illness, injection site reactions, myalgia, nausea, pyrexia.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of the vaccine was assessed in a Pooled Safety Analysis of 10 different controlled and uncontrolled phase 3 clinical studies in which 4,043 healthy adults aged 18 to 86 years received at least one dose of IXIARO*.

Non-study population: pregnant and nursing women, persons younger than 18 years, persons with any underlying disease.

Common Adverse Reactions from Clinical Trials after primary immunisation or booster doses

Most commonly reported adverse reactions (Treatment Emergent Adverse Events [TEAEs], assessed as probably or possibly related by the investigator) included headache and myalgia, occurring in approximately 20% and 13% of subjects, respectively. The adverse reactions with frequency ≥1% seen in clinical trials are described in Table 2.

Table 2: Adverse Reactions occurring in ≥1% of subjects who received IXIARO*: Pooled Safety Analysis

System organ class and preferred term	IXIARO* N=4043	
	n	**(%)**
Nervous system disorders	**806**	**(19.94)**
Headache	779	(19.27)
General Disorders and Administration Site Conditions	**738**	**(18.25)**
Fatigue	395	(9.77)
Influenza Like Illness	363	(8.98)
Pyrexia	84	(2.08)
Musculoskeletal and Connective Tissue Disorders	**541**	**(13.38)**
Myalgia	524	(12.96)
Gastrointestinal Disorders	**228**	**(5.64)**
Nausea	193	(4.77)

Local Tolerability

Local tolerability (pain, itching, tenderness, hardening, swelling, redness) was documented in a subject diary for seven consecutive days after each vaccination (inclusively) in studies IC51-301, IC51-302, IC51-304, IC51-309 IC51-310 and IC51-314. Tenderness was not collected in subject diaries of clinical study IC51-304.
The frequency of local symptoms of any (mild, moderate, severe or missing) severity within days 0-6 after the vaccination at day 0, vaccination at day 28 and after any vaccination are presented in Table 3.

Table 3: Local tolerability after any vaccination by symptom (mild, moderate, severe or missing severity) within Days 0-6, Pooled Safety Analysis

Local tolerability symptom	Days 0-6 n (N,%)
Pain	1334 (4016, 33.2%)
Tenderness	1210 (3642, 33.2%)
Redness	373 (4016, 9.3%)
Hardening	332 (4016, 8.3%)
Swelling	195 (4016, 4.9%)
Itching	140 (4016, 3.5%)

n=diary periods with at least one diary day with symptom, N=diary periods with at least one non-missing diary entry for symptom, %=n/N

Less Common Adverse Reactions from Clinical Trials after primary immunisation or booster doses

Table 4: Adverse Reactions occurring in <1% of subjects, condensed after medical review: Pooled Safety Analysis

System organ class and preferred term	IXIARO* N=4043	
	n	(%)
Nervous System Disorders		
Dizziness	16	(0.40)
Migraine	11	(0.27)
Paraesthesia	3	(0.07)
General Disorders and Administration Site Conditions		
Injection site haematoma	27	(0.67)
Chills	5	(0.12)
Malaise	5	(0.12)
Oedema peripheral	1	(0.02)
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal stiffness	5	(0.12)
Pain in extremity	3	(0.07)
Arthralgia	2	(0.05)
Gastrointestinal Disorders		
Vomiting	27	(0.67)
Diarrhea	23	(0.57)
Abdominal Pain	4	(0.10)
Infections and infestations		
Nasopharyngitis	33	(0.82)
Rhinitis	15	(0.37)
Skin and Subcutaneous Tissue Disorders		
Pruritus	4	(0.10)
Erythema	3	(0.07)
Urticaria	1	(0.02)
Rash	39	(0.96)
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	2	(0.05)
Investigations		
Hepatic Enzyme Increased	9	(0.22)
Blood and Lymphatic System Disorders		
Lymphadenopathy	8	(0.20)
Thrombocytopenia	1	(0.02]
Ear and Labyrinth Disorders		
Vertigo	16	(0.40)
Cardiac Disorders		
Palpitations	2	(0.05)
Tachycardia	2	(0.05)

Serious Adverse Events

Summary of Serious Adverse Events reported in Clinical Trials

91 serious adverse events were reported in 4248 subjects who received IXIARO* in 10 clinical trials. Causality was assessed by investigator as not related or unlikely related in the SAEs summarized below and in table 5.

Accidents and surgical procedures: 22 events

Cancer: 8 events
Cancer of colon, pancreas, breast (2 events), lung, ovary, prostate, chondroma

Gastro-intestinal disorders: 10 events
Abdominal pain (2 events), acute abdomen, appendicitis (2 events), cholecystitis, diverticulitis, rectal hemorrhage, gastrointestinal infection, reflux oesophagitis

Genitourinary disorders: 14 events
Cervix disorder, ectopic pregnancy, nephrolithiasis, ruptured ovarian cyst (3 events), ovarian torsion, renal colic, urinary incontinence, vaginal cyst, non-infective cystitis, endometrial hyperplasia, menorrhagia, ureteric stenosis

Infections: 13 events
Soft tissue abscess (2 events), erysipelas, herpes zoster, peritonsillar abscess, pneumonia, pyelonephritis, respiratory tract infection, appendiceal abscess, tubo-ovarian abscess, anal abscess, tonsillitis, shingles

Nervous System Disorders: 3 events
Convulsion, epilepsy, carotid artery stenosis

Others: 12 events
Drug toxicity, musculoskeletal pain (2 events), bone marrow donation, retinal detachment, stillbirth, mediastinal mass, hallux rigidus left, surgical correction of deviated nasal septum, bursitis, anaemia, endometritis

Vascular or cardiac disorders: 6 events
Chest pain (2 events), intracranial aneurysm, myocardial infarction, thrombosis, coronary artery stenosis

The following medically relevant serious adverse events were reported:

Table 5: Medically relevant serious adverse events in clinical trials

Event	Interval to vaccination	Outcome	Causality assessment by investigator	Comment
CSF cell count increased[#]	40 days	No symptoms by time of last follow up	Unlikely related	Cause not established
Dermatomyositis	12 days	Ongoing by time of last follow up	Unlikely related	Pre-existing condition

[#] *2 events in 1 subject; initial symptom: ocular fixation difficulties*

In addition, two serious adverse events assessed as possibly related were reported.

Table 6: Serious Adverse Events assessed as possibly or probably related to vaccination in or as follow-up to clinical trials completed and ongoing to date

Event	Interval to vaccination	Outcome	Causality assessment by Investigator
Syndactyly[#]	8.5 months[##]	not recovered	possibly related
Hypertension	12 days	recovered	possibly related

[#] *Syndactyly of 2nd and 3rd toes, in infant of vaccinated subject*

[##] *Delivery 8.5 months after vaccination. Estimated interval between last menstrual period and last IXIARO* vaccination was 5 weeks.*

Abnormal Hematologic and Clinical Chemistry Findings

There were no safety concerns with regard to haematological parameters, clinical chemistry or urinalysis across studies. Increased hepatic enzymes occurred in <1% of subjects, there was no safety concern associated.

Post-Market Adverse Drug Reactions

The following serious unexpected adverse drug reactions 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 (see Table 7).

Table 7: Serious unexpected Post-Market Adverse Drug Reactions

Adverse Drug Reaction	Interval to vaccination	Outcome
Iritis	4 days	Not reported
Epilepsy	4 minutes	Recovered
Oropharyngeal spasm	Same day	Recovered
Herpes zoster	5-7 days	Not yet recovered
Convulsion	Same day	Recovered
Cerebral infarction	< 1 day	Recovering
Convulsion	< 1 day	Not reported
Convulsion	Not reported	Not reported
Convulsion	1 min	Recovered
Pain in extremity	< 1 day	Recovering
Syncope	2 d /3 mo	Recovered
Labyrinthitis	< 1 day	Recovering

DRUG INTERACTIONS

Overview

Not applicable.

Use with other vaccines:

Concomitant administration of IXIARO* with inactivated hepatitis A vaccine has been evaluated in one clinical study. There was no interference with the immune response to JEV and HAV vaccines, respectively. Concomitant administration of IXIARO* and hepatitis A vaccine was shown to be non-inferior to single vaccinations with regard to geometric mean

titres (GMT) of anti-JEV neutralizing antibody and HAV antibody, and for seroconversion rates.
There were no statistically significant higher rates in systemic or local tolerability symptoms among subjects who received concomitant vaccination with IXIARO* and hepatitis A vaccine compared with those who received IXIARO* or hepatitis A vaccine alone.
The most frequently reported local tolerability symptom on the day of the first vaccination in all three groups was injection site pain in 59.0% of subjects receiving IXIARO* + HAVRIX, in 48.4% of subjects receiving IXIARO* + placebo vaccine and in 48.4% of subjects receiving HAVRIX + placebo vaccine. The second most frequent symptom was tenderness in 45.9%, 43.8% and 42.2% of subjects, respectively.
If co-administration with another vaccine is indicated, immunisation should be carried out on separate limbs.

Drug-Drug Interactions
Interactions with other drugs have not been established.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions
No studies on the effect of IXIARO* on the ability to drive or use machines have been performed.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Not applicable.

Recommended Dose and Dosage Adjustment
The primary vaccination series consists of two separate doses of 0.5 mL each according to the following schedule:
First dose at Day 0.
Second dose: 28 days after first dose.
A seroconversion rate of 29.4% has been observed 10 days after the first vaccination, and 97.3% one week after the second vaccination. Hence the primary immunization should be completed at least one week prior to potential exposure to Japanese encephalitis virus (JEV).
It is recommended that vaccinees who received the first dose of IXIARO* complete the primary 2-dose vaccination course with IXIARO*.

Missed Dose

If the primary vaccination series of two injections is not completed, full protection against the disease might not be achieved.
There is data that a second injection given up to 11 months after the first dose results in high seroconverion rates. Seroconversion rate was 99.0% (99/100; GMT 504.3 [95% CI: 367.3, 692.3]) at 1 month after the second vaccination at Month 11 and was 88.5% (85/96; GMT 121.0 [95% CI: 87.4, 167.6]) by Month 24. For details see Part II – Scientific Information.

Booster Dose

A booster dose (third dose) should be given within the second year (i.e. 12 - 24 months) after the recommended primary immunization, prior to potential re-exposure to JEV. Persons at continuous risk for acquiring Japanese encephalitis (laboratory personnel or persons residing in endemic areas) should receive a booster dose at month 12 after primary immunization. For details see Part II – Scientific Information. Data on the need for further booster doses are not available.

Administration

The vaccine should be administered by intramuscular injection into the deltoid muscle. It should never be injected intravascularly.
Exceptionally, IXIARO* may also be administered subcutaneously to patients with thrombocytopenia or bleeding disorders since bleeding may occur following an intramuscular administration. Subcutaneous administration could lead to a suboptimal response to the vaccine. However, it should be noted that there are no clinical efficacy data to support administration by the subcutaneous route.
Each pre-filled syringe is for single use only and should not be used for more than one individual. Inject the entire contents of the syringe.

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

OVERDOSAGE

No case of overdose has been reported.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Disease Burden

Japanese Encephalitis is one of the most common viral encephalitis with over 50,000 cases reported worldwide annually, although the figure could be much higher due to the lack of proper surveillance systems in many Asian countries where the virus is endemic. JEV is a mosquito-borne flavivirus; humans are an accidental host and are not considered reservoirs

for virus transmission. The majority of infections in humans are asymptomatic, and overt encephalitis occurs in only one out of every 50 to 1,000 individuals infected. JE disease has an associated mortality rate of 30-40%, and 50% of affected patients are left with permanent neuropsychiatric sequelae. Hence, although the relative mortality rate in a healthy population might be very low, due to the permanent neurological sequelae, the public health burden for the society is much higher.
Visitors to areas where JE is endemic or epidemic are at higher risk of being infected with JE compared to the local population. Incidence rates for JE disease in non-immunized Western troops have been observed to reach up to 2 per 10,000 individuals per week [4]. Sporadic cases of JE disease in travellers from Europe and North America are reported every year.

Mechanism of Action

Studies in animals have shown that the vaccine triggers the immune system to produce antibodies against Japanese encephalitis virus that are most often protective. Challenge studies were performed in mice that were treated with human IXIARO* antisera. These studies showed that almost all mice that had a Plaque Reduction Neutralization Test titre of at least 1:10 were protected from a lethal Japanese encephalitis virus challenge. These studies suggest that protection is mediated by antibodies raised against the vaccine.

Antibody persistence

Antibody persistence was evaluated in an uncontrolled Phase 3 follow up clinical trial, enrolling subjects who had completed two pivotal trials, and who received at least one dose of IXIARO*. Long term immunogenicity of IXIARO* was assessed in a subset of 181 subjects up to month 24 (ITT Population) and in 152 subjects up to month 36 after the first IXIARO* vaccination. Rates of subjects with $PRNT_{50} \geq 1:10$ and GMTs at Month 2, 6, 12, 24 and 36 are summarized in Table 8.

Table 8: SCR and GMT at Month 2, 6, 12, 24 and 36 after vaccination with IXIARO* – results from a pivotal long-term immunogenicity study

Month	SCR		GMT	
	% (n/N)	95% Confidence Interval		95% Confidence Interval
2	98.9 (179/181)	[96.1, 99.7]	310.8	[268.8, 359.4]
6	95.0 (172/181)	[90.8, 97.4]	83.5	[70.9, 98.4]
12	83.4 (151/181)	[77.3, 88.1]	41.2	[34.4, 49.3]
24	81.8 (148/181)	[75.5, 86.7]	44.3	[36.7, 53.4]
36	84.9 (129/152)	[78.3, 89.7]	43.8	[36.5, 52.6]

In another open-label, follow-up Phase 3 study, antibody persistence up to 24 months after primary vaccination was assessed. The primary endpoint was the SCR at 24 months after the primary vaccination. A total of 118 subjects who had received the standard schedule of IXIARO* were included in the follow-up study. SCRs and GMTs at Month 24 are summarized in Table 9 for the ITT population.

Table 9: SCR and GMT at Month 6, 12 and 24 after vaccination with IXIARO* – results from a supporting long term persistence study

Month	SCR		GMT	
	% (n/N)	95% Confidence Interval		95% Confidence Interval
6	82.8 (96/116)	[74.9, 88.6]	46.6	[38.7, 56.1]
12	58.3 (67/115)	[49.1, 66.9]	18.0	[15.5, 20.8]
24	48.3 (56/116)	[39.4, 57.3]	16.2	[13.8, 19.0]

STORAGE AND STABILITY

Store in a refrigerator (2°C - 8°C). Do not freeze.
Store in the original package to protect from light.
Do not use after the expiry date shown on the label.

SPECIAL HANDLING INSTRUCTIONS

Do not use if the blister foil is not intact or packaging is damaged.
Upon storage, a fine white deposit with a clear colorless supernatant can be observed.
Do not use if the product appears discolored (i.e. off-white) or if the syringe is damaged.
The pre-filled syringe is ready to use. If a needle is not provided, use a sterile needle. 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.**

Shake before use. Thorough agitation immediately before administration is necessary to maintain suspension of the vaccine. The full recommended dose of the vaccine should be used.
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 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.
Any unused product or waste material should be disposed of in accordance with local requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage form

Suspension for injection.

Composition

A single dose (0.5 mL of sterile suspension) of IXIARO* contains:
6 micrograms (protein content) of inactivated Japanese encephalitis virus (attenuated strain SA_{14}-14-2 produced in Vero cells) adsorbed on aluminum hydroxide, hydrated (0.25 mg Al/dose).

Packaging

0.5 mL of sterile suspension in a pre-filled syringe (Type I glass) with a plunger stopper

(halobutyl elastomer).
Pack size of 1 syringe with or without a separate needle.

* Registered Trademark

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance
Proper name: Japanese encephalitis purified inactivated virus (JE-PIV)

Product Characteristics
IXIARO* is a purified and inactivated Japanese encephalitis virus (JEV) vaccine. The virus is grown in Vero cells, purified, inactivated, and then adsorbed on aluminium hydroxide. The final vaccine is in the form of a suspension in a pre-filled syringe. Each unit dose of IXIARO* contains 6 mcg of the inactivated JEV, strain SA_{14}-14-2 per 0.5 mL. The vaccine does not contain any preservative or antibiotic. The vaccine is stored at 2-8°C. After thorough agitation, IXIARO* is a white, cloudy suspension.

CLINICAL TRIALS

Study Demographics and Trial Design
Two pivotal and 8 supporting phase 3 clinical studies have been conducted to gather efficacy (immunogenicity) and safety data of IXIARO*. Two of these clinical studies are ongoing.

Seroconversion
The analysis of clinical efficacy was done using a cutoff of a neutralizing antibody titre of ≥1:10, which was also used as a criterion for Seroconversion. Seroconversion or the threshold antibody level for protection is defined as a $PRNT_{50}$ titre ≥ 1:10, as recommended by the World Health Organization (WHO) consultation group and is widely used worldwide. Experiments done in mice also confirmed the above mentioned fact.The PRNT or Plaque neutralization assay, measures virus neutralizing antibody that correlates with protection. The virus neutralising antibody titre is expressed as the serum dilution giving a 50% plaque or virus reduction ($PRNT_{50}$) compared to 100% plaque formation in virus only control. All $PRNT_{50}$ results are expressed as reciprocal titres. GMT was defined as the geometric mean of $PRNT_{50}$ titres.

Pivotal Efficacy Study: IC51-301

Table 10: Trial Design and Demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
IC51-301	Randomized, active-controlled, observer-blinded, non-inferiority (IXIARO* vs. JE-VAX), phase 3 study	2 injections of IXIARO* (6 mcg in 0.5mL) intramuscularly (i.m.) on days 0 and 28 and 1 i.m. injection of 0.5mL placebo vaccine at Day 7 (Group A) or 3 subcutaneous injections of JE-VAX (1.0mL dose) on Day 0, 7 and 28 (Group B). Study duration: 6 months	IXIARO*: n=365 JE-VAX: n=370	IXIARO*: 41.2 years (18-78) JE-VAX: 41.2 years (18-80)	IXIARO*: 133 Male (M)/232 Female (F) JE-VAX: 152M/218 F

Demographic characteristics and baseline laboratory values were similar between the groups and are presented for the safety population.
Overall, 80.8% of the subjects were Caucasian, 13.1% were African American, 5.3% were "Other" and 0.8% were Asian. Overall, 77.8% of the subjects had negative anti-flavivirus immune status at baseline; 12.4% of the subjects had received TBE vaccination within the last 10 years and 34.4% had received any vaccination within the last 3 years. Notably, a higher proportion of subjects with positive baseline anti-flavivirus status in Europe (60.7% of 201 subjects) compared with North America (7.7% of 662 subjects) were observed.

Results

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

Table 11: SCR and GMT of IXIARO* and JE-VAX – Primary Endpoints

Primary Endpoints	Associated value and statistical significance for IXIARO* at specific time points	Associated value and statistical significance for JE-VAX or active control
To demonstrate the non-inferiority of IXIARO* (2 x 6 mcg) compared to JE-VAX (3 x 1.0 mL) in terms of the seroconversion rate (SCR) and geometric mean titre (GMT) at Day 56; four weeks after the last vaccination.	**SCR [N=365, n (%)]** Day 0 (Screening): 0 Day 28: 197 (54.0) Day 56: 352 (96.4) **GMT [N=365]** Day 0 (Screening): 5 Day 28: 17.4 Day 56: 243.6	**SCR [N=370, n (%)]** Day 0 (Screening): 0 Day 28: 321 (86.8) Day 56: 347 (93.8) **GMT [N=365]** Day 0 (Screening): 5 Day 28: 76.9 Day 56: 102.0

Risk difference estimate [95% CI]:Day 56: 1.05 [-1,33, 3.43]

Table 12: Immunogenicity Results of Study IC51-301 in Specific Indication – Secondary Endpoints

Secondary Endpoints	Associated value and statistical significance for IXIARO* at specific dosages	Associated value and statistical significance for JE-VAX or active control
SCR and GMT in subjects aged <50 and ≥50.	SCR <50 years: 284/301 (94.4%) SCR ≥50 years: 113/129 (87.6%)	SCR <50 years: 273/304 (89.8%) SCR ≥50 years: 120/133 (90.2%)
SCR and GMT in subjects aged <65 versus ≥65 years, post-hoc analysis	SCR <65 years: 328/337 (96.5%) SCR ≥65 years: 24/25 (96.0%)	SCR <65 years: 326/341 (94.0%) SCR ≥65 years: 21/23 (91.3%)
Adverse events (AEs)	In the safety population 61.0% experienced at least one TEAE (treatment emergent adverse event). No deaths were reported. One subject in the IXIARO* group experienced a serious adverse event (SAE) of myocardial infarction which was severe in intensity and unlikely related to study treatment. This subject had a history of myocardial infarction. In general, the systemic tolerability profile was similar between IXIARO* and JE-VAX. Systemic symptoms were most common one day after vaccination, decreasing over time for both treatment groups.	In the safety population 60.7% experienced at least one TEAE (treatment emergent adverse event). No deaths were reported. No serious adverse events (SAEs) were reported. In general, the systemic tolerability profile was similar between IXIARO* and JE-VAX. Systemic symptoms were most common one day after vaccination, decreasing over time for both treatment groups.

Table 13: Possibly or probably related Treatment Emergent Adverse Events:

TEAE system organ class[1] and preferred term[2]	n(%) of subjects			
	IXIARO* N=428		JE-VAX N=435	
	n	(%)	n	(%)
Any TEAE	**159**	**(37.1)**	**149**	**(34.3)**
Gastrointestinal disorders	**21**	**(4.9)**	**29**	**(6.7)**
Diarrhoea	2	(0.5)	3	(0.7)
Nausea	20	(4.7)	26	(6.0)
Vomiting	3	(0.7)	2	(0.5)
General disorders and administration site conditions	**80**	**(18.7)**	**73**	**(16.8)**
Fatigue	41	(9.6)	35	(8.0)
Influenza like illness	37	(8.6)	30	(6.9)
Pyrexia	16	(3.7)	10	(2.3)
Infections and infestations	**2**	**(0.5)**	**4**	**(0.9)**
Nasopharyngitis	1	(0.2)	3	(0.7)
Musculoskeletal and connective tissue disorders	**65**	**(15.2)**	**54**	**(12.4)**
Myalgia	65	(15.2)	52	(12.0)
Nervous system disorders	**76**	**(17.8)**	**80**	**(18.4)**
Headache	74	(17.3)	79	(18.2)
Respiratory, thoracic and mediastinal disorders	**5**	**(1.2)**	**2**	**(0.5)**
Skin and subcutaneous tissue disorders	**5**	**(1.2)**	**7**	**(1.6)**
Rash	3	(0.7)	5	(1.1)

Source: Clinical Study Report, Section 14, Table 4.2.5
[1] Only includes SOCs in which TEAEs were reported in ≥0.5% subjects overall
[2] Preferred terms only given for TEAEs occurring in ≥0.5% subjects overall
Treatment related is possibly or probably related

Table 14: Subject Diary Local Tolerability One Day (Day 1) After Vaccination: Safety Population

Symptom		IXIARO* N=428		JE-VAX N=435	
		n	(%)	n	(%)
Pain	Vaccination 1	46	(10.7)	32	(7.4)
	Vaccination 2[#]	28	(6.5)	32	(7.4)
	Vaccination 3	19	(4.4)	29	(6.7)
Itching	Vaccination 1	3	(0.7)	22	(5.1)
	Vaccination 2[#]	2	(0.5)	29	(6.7)
	Vaccination 3	4	(0.9)	34	(7.8)
Tenderness	Vaccination 1	82	(19.2)	54	(12.4)
	Vaccination 2[#]	55	(12.9)	75	(17.2)
	Vaccination 3	54	(12.6)	75	(17.2)
Hardening	Vaccination 1	13	(3.0)	24	(5.5)
	Vaccination 2[#]	6	(1.4)	36	(8.3)
	Vaccination 3	9	(2.1)	46	(10.6)
Swelling	Vaccination 1	4	(0.9)	18	(4.1)
	Vaccination 2[#]	5	(1.2)	20	(4.6)
	Vaccination 3	4	(0.9)	36	(8.3)
Redness	Vaccination 1	8	(1.9)	34	(7.8)
	Vaccination 2[#]	4	(0.9)	49	(11.3)
	Vaccination 3	8	(1.9)	61	(14.0)

Source: Clinical Study Report, Section 14, Table 4.4.6
[#]IXIARO group: Vaccination 2 was placebo vaccine*

Local tolerability symptoms were most common one day after vaccination, decreasing over time for both treatment groups.

Pivotal Safety Study: IC51-302

Table 15: Trial Design and Demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
IC51-302	Randomized, placebo-controlled, double-blind, multi-centre safety and tolerability, phase 3 study	2 injections of IXIARO* (6 mcg in 0.5mL) intramuscularly (i.m.) on days 0 and 28 (Verum group) or 2 injections of placebo vaccine (0.5 mL) intramuscularly on days 0 and 28 (Control group). Study duration: 6 months	Verum group: n=1993 Control group: n=657	Verum group: 33.9 years (18-86) Control group: 33.4 years (18-76)	Verum group: 905M/1088F Control group: 279M/378F

The two treatment groups were well matched for demographic characteristics. Brief narrative is presented for the safety population.
The most common race was Caucasian (91.7%) followed by African American (3.4%), Asian (1.8%), and Other (3.0%).

Results

Table 16: Results of Study IC51-302 in Specific Indication – Primary Endpoints

Primary Endpoints	Associated value and statistical significance for IXIARO* at specific dosages	Associated value and statistical significance for Placebo vaccine or active control
To investigate the safety and tolerability of IXIARO* during a vaccination period of 28 days until 4 weeks after the last vaccination compared with an inactive control.	During the total study period, 58.9% of subjects experienced at least one TEAE.	During the total study period, 56.6% of subjects experienced at least one TEAE.

Table 17: Results of Study IC51-302 in Specific Indication – Secondary Endpoints

Secondary Endpoints	Associated value and statistical significance for IXIARO* at specific dosages	Associated value and statistical significance for Placebo vaccine or active control
To analyze the rates of serious adverse events (SAEs) and medically attended adverse events (AEs) in individuals before and after immunization with IXIARO*.	No deaths occurred in this study. A total of 16 subjects who experienced serious TEAEs during the total study period, ten (0.5%) subjects in the IXIARO* group. No serious TEAEs occurred in more than 0.3% of subjects overall in any SOC There were no treatment-related serious TEAEs.	No deaths occurred in this study. A total of 16 subjects who experienced serious TEAEs during the total study period, six (0.9%) subjects in the placebo vaccine group. No serious TEAEs occurred in more than 0.3% of subjects overall in any SOC, only appendicitis which occurred in more than 1 subject, i.e., in 2 subjects. There were no treatment-related serious TEAEs.

Table 18: Possibly or probably related Treatment Emergent Adverse Events (Total Study Period) – Safety Population

TEAE system organ class[1] and preferred term[2]	n (%) of subjects			
	IXIARO* N=1993		Placebo vaccine N=657	
	n	(%)	n	(%)
Any TEAE	**774**	**(38.8)**	**254**	**(38.7)**
Blood and lymphatic system disorders	**10**	**(0.5)**	**4**	**(0.6)**
Gastrointestinal disorders	**117**	**(5.9)**	**39**	**(5.9)**
Nausea	101	(5.1)	36	(5.5)
Vomiting	13	(0.7)	7	(1.1)
General disorders and administration site conditions	**343**	**(17.2)**	**119**	**(18.1)**
Fatigue	188	(9.4)	65	(9.9)
Influenza like illness	178	(8.9)	57	(8.7)
Pyrexia	47	(2.4)	15	(2.3)
Infections and infestations	**42**	**(2.1)**	**9**	**(1.4)**
Nasopharyngitis	15	(0.8)	4	(0.6)
Investigations	**20**	**(1.0)**	**3**	**(0.5)**
Musculoskeletal and connective tissue disorders	**276**	**(13.8)**	**101**	**(15.4)**
Myalgia	271	(13.6)	94	(14.3)
Nervous system disorders	**439**	**(22.0)**	**134**	**(20.4)**
Dizziness	8	(0.4)	4	(0.6)
Headache	428	(21.5)	131	(19.9)
Respiratory, thoracic and mediastinal disorders	**17**	**(0.9)**	**8**	**(1.2)**
Pharyngolaryngeal pain	9	(0.5)	5	(0.8)
Skin and subcutaneous tissue disorders	**26**	**(1.3)**	**8**	**(1.2)**
Rash	18	(0.9)	4	(0.6)

Source: *Section 14, Table 4.2.6.1*

[1] *Only includes SOCs in which treatment-related TEAEs were reported in ≥0.5% subjects overall*

[2] *Preferred terms only given for treatment-related TEAEs occurring in ≥0.5% subjects overall*

N=number of subjects in group; n (%) = number and percentage of subjects affected (subjects are only counted once per line); TEAE=treatment emergent adverse event

Treatment-related is possibly or probably related or missing

Table 19: Subject Diary Local Tolerability One Day (Day 1) After Vaccination – Safety Population

Symptom reported		IXIARO* N=1993		Placebo vaccine N=657	
		n	(%)	n	(%)
Pain	Vaccination 1	369	(18.5)	102	(15.5)
	Vaccination 2	210	(10.5)	62	(9.4)
Itching	Vaccination 1	15	(0.8)	11	(1.7)
	Vaccination 2	15	(0.8)	8	(1.2)
Tenderness	Vaccination 1	414	(20.8)	114	(17.4)
	Vaccination 2	295	(14.8)	79	(12.0)
Hardening	Vaccination 1	55	(2.8)	24	(3.7)
	Vaccination 2	49	(2.5)	12	(1.8)
Swelling	Vaccination 1	24	(1.2)	14	(2.1)
	Vaccination 2	28	(1.4)	3	(0.5)
Redness	Vaccination 1	65	(3.3)	23	(3.5)
	Vaccination 2	58	(2.9)	10	(1.5)

N=number of subjects in group; n=number of subjects with data; %=percentage of subjects based on number of patients in the group
Source: Section 14, Table 4.4.7

Local symptoms were most common on Day 0, decreasing over time for both treatment groups. For all symptoms the incidence on Day 1 after vaccination was slightly higher in the IXIARO* group for both vaccinations, with the exception of itching (0.8%) after vaccination 1 and 0.8% subjects after vaccination 2, hardening (2.8% after vaccination 1), swelling (1.2% after vaccination 1) and redness (3.3% after vaccination 1).

Supporting Study: IC51-303

Table 20: Trial Design and Demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
IC51-303	Prospective, multi-center, uncontrolled phase 3 follow-up study	No treatment given. Follow-up to IC51-301 and IC51-302 . Study duration: Follow-up for up to 60 months for immunogenicity and safety ongoing, 36 months data available to date.	Months 6, 12 and 24 (ITT): 181 ITT population Month 36: 152	Months 6, 12 and 24 (ITT): 32.1 (18-74) ITT Month 36: 30.9 (18-67)	ITT Months 6, 12 and 24 85M/96F Month 36: 57M/74F

Most of the subjects included were Caucasian (98.3% of subjects); other races were Black or African American (0.6%), Asian (0.0%) and Other (1.1%).

Interim Results

This ongoing study is following-up on long-term immunogenicity up to 60 months, 36- month interim results are available.
The first 298 subjects reaching Day 1 of study IC51-303 who were willing to participate in

the immunogenicity part of the study were enrolled in the long-term immunogenicity study. Following the database lock for studies IC51-301 and IC51-302, subjects with negative plaque reduction neutralization assays (PRNT) or had received JE-VAX or placebo vaccine were discontinued.

Table 21: Interim Results of Study IC51-303 in Specific Indication – Primary Endpoints

Primary Endpoints	**Associated value and statistical significance for IXIARO* at specific time points** **SCR [N=181, n (%)]**	**Associated value and statistical significance for JE-VAX or active control**
SCR (anti-JEV neutralizing antibody titre ≥1:10) 24 months after the first vaccination	SCR at Month 24 : 148 (81.8%), 95% CI [75.50, 86.71]	Not applicable

Table 22: Interim Results of Study IC51-303 in Specific Indication – Secondary Endpoints

Secondary Endpoints	**Associated value and statistical significance for IXIARO* at specific dosages**	**Associated value and statistical significance for JE-VAX or active control**
SCR and GMTs 36 months after the first vaccination.	*SCR, n/N (%) [95% CI, %]* 129/152 (84.9) [78.32, 89.7] *GMT (n) [95% CI]* 43.8 (152) [36.5, 52.6]	Not applicable
GMTs for anti-JEV neutralizing antibody 24 months after the first vaccination.	*GMT (n) [95% CI]* Month 24: 44.3 (181) [36.72, 53.44]	Not applicable
SCR and GMT 12 months after the first vaccination.	*SCR, n/N (%) [95% CI, %]* 151/181 (83.4) [77.33, 88.14] *GMT (n) [95% CI]* 41.2 (181) [34.39, 49.33]	Not applicable
SCR and GMT 6 months after the first vaccination.	ITT population, IXIARO* only (imputed values): *SCR, n/N (%) [95% CI, %]* 172/181 (95.0) [90.82, 97.36] Risk difference estimate for SCRs (IXIARO*-JE-VAX), [95%CI]: 17.81 [6.75, 28.86] *GMT (n) [95% CI]* 83.5 (181) [70.89, 98.38] *GMT rati*o (IXIARO*-JE-VAX) [95% CI]*:* 2.2632 [1.6151, 3.1714]	Treatment comparison, ITT3 population (imputed values) SCR, n/N (%) [95% CI, %]: 61/82 (74.4%) [64.00, 82.60] GMT (n) [95% CI] 34.1 (82) [25.11, 46.44]

Supporting Study: IC51-304

Table 23: Trial Design and Demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
IC51-304	Prospective, multi-center, observer-blind, randomized (1:1:1), parallel-group, phase 3 study	IXIARO* 12 mcg (2 x 6 mcg i.m. injections) on Day 0 (and placebo vaccine on Day 28) IXIARO* 6 mcg i.m. injection, Days 0 and 28 (and placebo vaccine on Day 0) IXIARO* 6 mcg i.m. injection on Day 0 (and placebo vaccine on Days 0 and 28) Study duration: 6 months	IXIARO* 1 x 12 mcg: 115 IXIARO* 2 x 6 mcg: 115 IXIARO* 1 x 6 mcg: 119	IXIARO* 1 x 12 mcg: 41.2 (18-76) IXIARO*2 x 6 mcg: 40.5 (18-74) IXIARO* 1 x 6 mcg: 41.7 (18-75)	IXIARO* 1 x 12 mcg: 54M/61F IXIARO* 2 x 6 mcg: 49M/66F IXIARO* 1 x 6 mcg: 62M/57F

The most common race was Caucasian (99.4% of subjects), followed by Asian (0.3%), and Black or African American (0.3%).

Results

Table 24: Results of Study IC51-304 in Specific Indication – Primary Endpoints

Primary Endpoints	Associated value and statistical significance for IXIARO* 2x6 mcg at specific timepoints SCR % (n/N) [95% CI]	Associated value and statistical significance for IXIARO* 1x12 mcg SCR% (n/N) [95% CI]
SCR (anti-JEV neutralizing antibody titre ≥1:10) at Day 56.	97.3 (110/113) [94.4, 100.0] *SCR difference (1x12 mcg minus 2x6 mcg)* *[95% CI]: -56.1 [-65.6, -46.6]* P-value (non-inferiority one-tailed test) : >0.99	41.2 (47/114) [32.2, 50.3]

Table 25: Results of Study IC51-304 in Specific Indication – Secondary Endpoints

Secondary Endpoints	Associated value and statistical significance for IXIARO* 2x6 mcg	Associated value and statistical significance for IXIARO* 1x12 mcg and IXIARO* 1x6mcg
SCR at Day 35	SCR % (n/N) [95% CI] 97.3 (110/113) [94.4, 100.0]	SCR % (n/N) [95% CI] IXIARO* 1 x 12 mcg: 58.8 (67/114) [49.7, 67.8] IXIARO* 1 x 6 mcg: 37.9 (44/116) [29.1, 46.8]
GMT for anti-JEV neutralizing antibody at Days 35 and 56	GMT (n) [95% CI] *Day 35* 265.82 (113) [214.19, 329.89] *Day 56* 218.04 (113) [179.81, 264.41]	GMT (n) [95% CI] *Day 35* IXIARO* 1 x 12 mcg: 17.62 (114) [14.21, 21.85] IXIARO* 1 x 6 mcg: 11.29 (116) [9.12, 13.97] *Day 56* IXIARO* 1 x 12 mcg: 11.21 (114) [9.25, 13.58] IXIARO* 1 x 6 mcg: 8.05 (117) [6.66, 9.74]

Supporting Study: IC51-305

Table 26: Trial Design and Demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
IC51-305	Prospective, multi-center, open-label, phase 3 follow-up study.	Follow-up to IC51-304 IXIARO* 6 mcg i.m. booster injection (0.5 ml) at Month 11 and/or Month 23 after primary vaccination in subjects with a negative PRNT result at Month 6 and/or Month 12 after primary vaccination Study duration: Follow-up up to Month 24 after first dose.	Randomized: IXIARO* 1 x 12 mcg: 116 IXIARO* 2 x 6 mcg: 116 IXIARO* 1 x 6 mcg: 117	IXIARO* 1 x 12 mcg: 42.2 (19-76) IXIARO* 2 x 6 mcg: 40.8 (19-74) IXIARO* 1 x 6 mcg: 42.0 (19-75)	IXIARO* 1 x 12 mcg: 57M/60F IXIARO* 2 x 6 mcg: 49M/67F IXIARO* 1 x 6 mcg: 59M/57F

The most common race was Caucasian (99.4% of subjects), followed by Asian (0.9%), and Black or African American (0.9%).

Results

Table 27: Results of Study IC51-305 in Specific Indication – Primary Endpoints

Primary Endpoints	**Associated value and statistical significance for IXIARO* 2x6 mcg at specific timepoints** **Seroconversion rate without booster, % (n/N) [95% CI]**	**Associated value and statistical significance for IXIARO* 1x12 mcg and IXIARO* 1x6mcg** **Seroconversion rate without booster, % (n/N) [95% CI]**
SCR without booster (anti-JEV neutralizing antibody titre ≥ 1:10 throughout study) 24 months after primary vaccination.	48.3 (56/116) [39.4, 57.3]	1x12 mcg: 6.0 (7/116) [3.0, 11.9] 1x6 mcg: 4.3 (5/117) [1.8, 9.6]

Table 28: Results of Study IC51-305 in Specific Indication – Secondary Endpoints

Secondary Endpoints	Associated value and statistical significance for IXIARO* 2x6 mcg	Associated value and statistical significance for IXIARO* 1x12 mcg and IXIARO* 1x6mcg
SCR one month after the booster doses in subjects with titres below the seroconversion threshold	SCR (n/N) [95%CI] Month 12 100% (17/17) [81.6, 100.0] Month 24 100% (27/27) [87.5, 100.0]]	SCR (n/N) [95%CI] Month 12 1x6 mcg group 99% (99/100) [94.6, 99.8] 1x12 mcg group 100% (89/89) [95.9,100.0] Month 24 1x6 mcg group 100% (4/4) [51.0,100.0] 1x12 mcg group 100% (12/12) [75.8,100.0]
GMT one month after the booster doses in subjects with titres below the seroconversion threshold	GMT (N) [95%CI] Month 12: 673.6 (17) [378.7, 1198.2] Month 24: GMT (27) 2536.7 [1467.7, 4384.4].	GMT (N) [95%CI] Month 12: 1x6 mcg group 504.3 (100) [367.3, 692.3] 1x12 mcg group 990.1 (89) [755.8,1297.0] Month 24: 1x6 mcg group 821.1 (4) [79.9, 8438.2] 1x12 mcg group 6622.8 (12) [3092.0, 14185]
SCR without booster and GMTs 6 and 12 months after primary vaccination	SCR: Month 6: 82.8% Month 12: 58.3% GMT: Month 6: 46.6 Month 12: 18.0	SCR: IXIARO* 1x12 mcg group: Month 6: 14.7% Month 12: 7.8% IXIARO* 1x6 mcg group: Month 6: 8.5% Month 12: 4.3% GMT: IXIARO* 1x12 mcg group: Month 6: 7.2 Month 12: 5.7 IXIARO* 1x6 mcg group: Month 6: 6.1 Month 12: 5.3

Supporting Study: IC51-311

Table 29: Trial Design and Demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
IC51-311	Multi-center, uncontrolled, open-label, phase 3 follow-up study.	Follow-up to IC51-309 IXIARO* 6 mcg i.m. booster injection (0.5 ml) at Month 15 after first vaccination. Study duration: Follow-up up to Month 12 after booster vaccination (Month 27 after first vaccination).	198	31.2 (19-66)	94M/104F

The most common race was Caucasian (98% of subjects), followed by Other (1%), Asian (0.5%), and Black or African American (0.5%).

Results

Table 30: Results of Study IC51-311 in Specific Indication – Primary Endpoints

Primary Endpoints	Associated value and statistical significance for IXIARO* 0.5ml booster dose at specific timepoint SCR % (n/N) [95% CI]
SCR (anti-JEV neutralizing antibody titre ≥1:10) at Month 12 after the booster vaccination (Month 27 after primary immunization).	98.5 (194/198) [95.6, 99.5]

Table 31: Results of Study IC51-311 in Specific Indication – Secondary Endpoints

Secondary Endpoints	Associated value and statistical significance for IXIARO* 0.5 ml booster dose at specific timepoints
SCR (anti-JEV neutralizing antibody titre ≥1:10) at Day 28 and Month 6 after the booster vaccination (Months 16 and 21 after first vaccination)	SCR % (n/N) [95% CI] *Day 0* 69.2 (137/198) [62.4, 75.2] *Day 28* 100 (198/198) [98.1, 100.0] *Month 6* 98.5 (197/198) [95.6, 99.5]
GMT for anti-JEV neutralizing antibody at Day 0, Day 28, Month 6 and Month 12 after the booster vaccination (Months 16, 21 and 27 after first vaccination)	GMT (n) [95% CI] *Day 0* 22.5 (198) [19.0, 26.7] *Day 28* 900.1 (198) [742.4, 1091.3] *Month 6* 487.4 (198) [390.7, 608.1] *Month 12* 361.4 (198) [294.5, 443.5]

Supporting Study: IC51-308

Table 32: Trial Design and Demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
IC51-308	Multi-center, single-blind, randomized (1:1:1), controlled phase 3 study	IXIARO* + HAVRIX: IC51 6 mcg i.m. (Days 0 and 28) and HAVRIX 1440 1ml i.m. (Day 0) IXIARO* +placebo vaccine: 6 mcg IC51 i.m. injection (Days 0 and 28) and 0.5 ml placebo vaccine i.m. (Day 0) HAVRIX+ placebo vaccine: HAVRIX 1440 1ml i.m. (Day 0) and 0.5 ml placebo vaccine i.m. (Days 0 and 28) Study duration: 6 months	IXIARO* + HAVRIX: 62 IXIARO* + placebo vaccine: 65 HAVRIX+ placebo vaccine: 65	IXIARO* + HAVRIX 27.6 (18.0-60.0) IXIARO* + placebo vaccine: 28.5 (19.0 to 51.0) HAVRIX+ placebo vaccine: 28.1 (19.0 to 61.0)	IXIARO* + HAVRIX 28M/34F IXIARO* + placebo vaccine: 31M/34F HAVRIX+ placebo vaccine: 30M/35F

At least 95% of subjects in each group were Caucasian; other races were Oriental, Asian, Caucasian/Black/African American, and Hispanic, all occurring in 2 subjects or less in any treatment group.

Results

Table 33: Results of Study IC51-308 in Specific Indication – Primary Endpoints

Primary Endpoints	**Associated value and statistical significance for IXIARO* + HAVRIX at specific time points**	**Associated value and statistical significance for IXIARO* + placebo vaccine and HAVRIX+ placebo vaccine**
GMT for anti-JEV neutralizing antibody at Day 56 and anti-HAV antibody at Day 28	*GMT (anti-JEV) Day 56, (n) [95% CI]:* IXIARO* +HAVRIX: 202.7 (58) [157.3, 261.2] GMT ratio estimate (p-value) [95% CI] IXIARO* +*HAVRIX/* IXIARO* + *placebo vaccine:* 1.0544 (<0.0001) [0.7541, 1.4743] *GMT (anti-HAV) Day 28, (n) [95% CI]:* IXIARO* + HAVRIX: 150.3 mIU/ml (58) [111.7 mIU/ml, 202.3 mIU/ml] GMT ratio estimate (p-value) [95% CI] IXIARO* +*HAVRIX/ HAVRIX +placebo vaccine:* 1.2127 (<0.0001) [0.8119, 1.8113] (<0.0001) [0.8115, 1.5041]	*GMT (anti-JEV) Day 56, (n) [95% CI]:* IXIARO* +placebo vaccine: 192.2 (55) [147.9, 249.8] *GMT (anti-HAV) Day 28, (n) [95% CI]:* HAVRIX + placebo vaccine: 124.0 mIU/ml (52) [91.4 mIU/ml, 168.2 mIU/ml]

Table 34: Results of Study IC51-308 in Specific Indication – Secondary Endpoints

Secondary Endpoints	**Associated value and statistical significance for IXIARO* + HAVRIX at specific time points**	**Associated value and statistical significance for IXIARO* + placebo vaccine and HAVRIX+ placebo vaccine**
SCR for Anti-JEV at Day 56 and Anti-HAV at Day 28	*Anti-JEV SCR, n/N (%)* IXIARO* + HAVRIX: 58/58 (100) SCR difference estimate, % (p-value) [95% CI, %]: 0.6% (p<0.0001) [-0.5, 1.7] *Anti-HAV SCR at Day 28, n/N (%):* IXIARO* + HAVRIX: 58/58 (100) SCR difference estimate, % (p-value) [95% CI, %]: 4.9 (p<0.0001) [-1.6, 11.5]	*Anti-JEV SCR, n/N (%)* IXIARO* + placebo: 54/55 (98.18) *Anti-HAV SCR at Day 28, n/N (%):* HAVRIX +placebo vaccine: 50/52 (96.2)
GMT for Anti-JEV at Day 28 and Anti-HAV at Day 56	*GMT (anti-JEV) Day 28, (n) [95% CI]:* IXIARO* +HAVRIX: 18.3 (58) [CI: 12.9, 26.0] GMT ratio estimate (p-value) [95% CI]: 1.1379 (p=0.0002) [0.7224, 1.7925] *GMT (anti-HAV) Day 56, (n) [95% CI]:* IXIARO* + HAVRIX: 102.0 mIU/ml (58) [76.9 mIU/ml, 135.2 mIU/ml] GMT ratio estimate (p-value) [95% CI]: 1.1652 (p<0.0001) [0.7958, 1.7060]	*GMT (anti-JEV) Day 28, (n) [95% CI]:* IXIARO* + placebo: 16.1 (58) [11.3, 22.9] *GMT (anti-HAV) Day 56, (n) [95% CI]:* HAVRIX+placebo vaccine: 87.5 mIU/ml (52)[65.5 mIU/ml, 117.0 mIU/ml]
SCR for Anti-JEV at Day 28 and Anti-HAV at Day 56	*Anti-JEV SCR at Day 28, n/N (%)* IXIARO* + HAVRIX: 39/58 (67.24) SCR difference estimate, % (p-value) [95% CI, %]: 0.1 (p<0.1086) [-16.0, 16.3] *Anti-HAV SCR at Day 56, n/N (%):* IXIARO* +HAVRIX: 55/58 (94.83) SCR difference estimate, % (p-value) [95% CI, %]: 0.3 (p=0.0064) [CI: -7.8, 8.5]	*Anti-JEV SCR at Day 28, n/N (%)* IXIARO* + placebo vaccine: 39/58 (67.24) *Anti-HAV SCR at Day 56, n/N (%):* HAVRIX+placebo vaccine: 50/52 (96.15)

Pooled Safety Analysis

Ten clinical trials (IC51-301, -302, -303, -304, -305, -308, -309, -310, -311 and -314) have been pooled for analysis of the safety and tolerability of IC51 during six months after the first vaccination.

Table 35: Overview of Treatment-Emergent Adverse Events

Subjects with at least	IXIARO*[#] (N=4043) No. (%)	JE-VAX (N=435) No. (%)	HAVRIX1440 (N=65) No. (%)	PLACEBO Vaccine (N=657) No. (%)
One TEAE	2657 (65.7)	279 (64.1)	31 (47.7)	402 (61.2)
One severe TEAE	272 (6.7)	19 (4.4)	3 (4.6)	42 (6.4)
One TEAE resulting in discontinuation of the study medication (=leading to withdrawal)	39 (0.97)	8 (1.8)	0	5 (0.8)
One serious TEAE	73 (1.8)	3 (0.7)	0	13 (2.0)
One TEAE with fatal outcome	1 (0.0)	0	0	0
One related TEAE	1557 (38.5)	149 (34.3)	12 (18.5)	255 (38.8)
One related severe TEAE	117 (2.9)	6 (1.4)	0	18 (2.7)
One related TEAE resulting in discontinuation of the study drug	17 (0.4)	4 (0.9)	0	1 (0.2)
One related serious TEAE	0	0	0	0
One related TEAE with fatal outcome	0	0	0	0

[#] *Data taken from two different pooled analyses*

Pediatric Studies

Pediatric Study IC51-221:

Table 36: Trial Design and Demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age	Gender
IC51-221	Single center, open label, active controlled phase 2 study, 2:2:1 randomization ratio, including children aged 1 to < 3 years	IXIARO* 6 mcg group: IC51 6 mcg i.m. (Days 0 and 28) IXIARO* 3 mcg group: 3 mcg IC51 i.m. injection (Days 0 and 28) Jencevac group: 0.5 ml s.c. (Day 0, 7 and 28) Study duration: 56 days	IXIARO* 6 mcg group: 24 IXIARO* 3 mcg group: 24 Jencevac group: 12	IXIARO* 3 mcg group: 1.7 IXIARO* 3 mcg group: 2.1 Jencevac group: 2.2	IXIARO* 3 mcg group: 14M/10F IXIARO* 3 mcg group: 14M/10F Jencevac group: 9M/3F

Table 37: Results of Study IC51-221 – Seroconversion rates

Visit	IXIARO* - 3 mcg (n = 24) n (%) [95% CI]	IXIARO* - 6 mcg (n = 24) n (%) [95% CI]	JenceVac™ (n = 12) n (%) [95% CI]	p-value[#]
Screening	1(4.2) [-3.8, 12.2]	1(4.2) [-3.8, 12.2]	0(0.0)	1.0000
Day 28	15(62.5) [43.1, 81.9]	15(62.5) [43.1, 81.9]	8(66.7) [40, 93.3]	1.0000
Day 56 Primary Endpoint	23(95.8) [87.8, 103.8]	23(95.8) [87.8, 103.8]	11(91.7) [76, 107.3]	1.0000

[#]*p-value obtained using Fisher-Freeman-Halton test.*

Table 38: Results of study IC51-221 – Geometric Mean Titres

Visit	IXIARO* - 3 mcg (n = 24) [95% CI]	IXIARO* - 6 mcg (n = 24) [95% CI]	JenceVac™ (n = 12) [95% CI]	p-value[#]
Screening	5.3 [4.7, 5.9]	5.2 [4.8, 5.7]	5 [4.4, 5.6]	0.7849
Day 28	23.5 [13, 42.6]	21.1 [12.1, 36.9]	25.9 [10.2, 66.1]	0.9096
Day 56	208.8 [113, 385.9]	216 [129.3, 361.1]	238.4 [78.8, 721.2]	0.9659

[#]*p-value obtained using ANOVA.*

Table 39: Safety results from study IC51-221

OVERVIEW OF AEs	IXIARO* - 3 mcg (n = 24)	IXIARO* - 6 mcg (n = 24)	JenceVac™ (n = 12)	p-Value[#]
Number of Adverse Events N (% against total events)	3 (23.1)	5 (38.5)	5 (38.5)	
Number of Subjects with at least one Adverse Event	3 (12.5)	5 (20.8)	4 (33.3)	0.2850
Fever	0 (0.0)	1 (4.2)	1 (8.3)	not done
Injection Site Tenderness	2 (8.2)	3 (12.5)	3 (25)	not done
Skin Lesion	1 (4.2)	0 (0.0)	0 (0.0)	not done
Skin Rash	0 (0.0)	1 (4.2)	0 (0.0)	not done

[#]*p-value obtained using Fisher-Freeman-Halton test.*

Comparative Bioavailability Studies

Not applicable.

DETAILED PHARMACOLOGY

Non-clinical pharmacology data

Pharmacodynamic Summary

Primary pharmacodynamic studies performed with IXIARO* included immunogenicity studies in mice, rats and rabbits. Active protection following immunization, passive protection following injection of immune sera from Phase 2 and Phase 3 clinical studies, and cross protection to different strains of JEV (namely JEV Beijing and JEV KE-093) was demonstrated for IXIARO* in lethal challenge studies in mice. The efficacy was based on the number of mice surviving 21 days after the JEV challenge. A dose-dependent increase in neutralizing antibody titre ($PRNT_{50}$ assay) which correlated with protection was demonstrated for IXIARO* in each of these studies.

In several non-clinical studies, JE-VAX was used as a comparator. JE-VAX is a Japanese encephalitis (JE) vaccine produced by a Japanese company, BIKEN (Research Foundation for Microbial Disease of Osaka University). The vaccine is manufactured using the virulent Nakayama-NIH virus strain, propagated in suckling mouse brains, purified and inactivated with formaldehyde. In addition to *in vivo* studies, cross-protection of IXIARO* and JE-VAX immune sera was evaluated *in vitro* using different JEV viruses in the PRNT (Plaque Reduction Neutralization Test) assay.

IXIARO* was immunogenic when administered by various routes in mice (s.c. and i.p. routes), rats (i.m.) and rabbits (i.m.). A dose-related increase in immunogenicity with IXIARO* could be clearly demonstrated.

The efficacy of IXIARO* was ascertained by challenge studies in mice, immunized twice, 2 weeks apart, with different concentrations of IXIARO* vaccine. This was followed by a challenge with a lethal dose of the wild-type JEV strain SA14.

The results demonstrated a dose-related increase in protection, i.e. immunization with higher doses of IXIARO* resulted in greater protection against lethal challenge.

In a second study, IXIARO* and JE-VAX were tested at various doses for protection in mice against challenge with a lethal dose of JEV strains SA14 and Beijing following a similar protocol as described above. IXIARO* was shown to protect mice in a dose dependent manner against both JEV strains. In addition, a. dose dependent relationship between vaccine dose and neutralizing antibody titre ($PRNT_{50}$) in both IXIARO* and JE-VAX treatment groups was observed.

Furthermore, comparison of GMT titres and survival demonstrates a direct relationship between the antibody titre and survival of mice. The overall conclusion of the described studies is that IXIARO* provided equal or better protection to mice against two JEV strains (SA14 and Beijing) than the currently licensed JEV vaccine, JE-VAX. IXIARO* doses of 0.6 to 36.4 mcg/kg bw provided 90% to 100% protection in mice against lethal challenge with JEV SA14. IXIARO* doses of 2.1 to 35.2 mcg/kg bw provided 90% to 100% protection in mice against lethal challenge with JEV Beijing.

The proposed dose for IXIARO* in humans is two injections of 6mcg each, and for an average adult of 60 kg body weight the comparative dose is 0.1mcg/kg body weight.

A passive immunization study was performed to test JEV antiserum obtained from human subjects vaccinated with IXIARO* or JE-VAX for the ability to confer protection against challenge with two wild-type JEV strains (SA14 or KE-093) in a JEV mouse model. Human sera were obtained from subjects who had taken part in clinical study IC51-301, a Phase 3 randomized, blinded non-inferiority study to compare the immunogenicity of IXIARO* against JE-VAX (*see Clinical Trials section*). IXIARO* immune sera were collected from

study subjects vaccinated with two doses of 6 mcg/0.5 mL IXIARO*. Serum was pooled into four batches based on antibody titre: high (measured pooled titre: 214), medium (43), low (21) and negative (non-responders, imputed to titre of 5).
Intermediate titre from subjects vaccinated with the recommended schedule of 3 doses of JE-VAX served as a positive control (55) and negative titre serum from subjects never vaccinated with a JEV vaccine served as a negative control.
Mice were given 0.5 mL of test serum, pre-diluted to either 1:2 or 1:10, via i.p. injection, followed 17-18 hours later by a challenge with a lethal dose of either JEV strain SA14 or KE-093.
Serum from human subjects vaccinated with IXIARO* successfully protected mice against lethal challenge with two different JEV strains in the highest titre groups. The protection offered in the intermediate titre groups was somewhat lower with the heterologous KE-093 challenge as compared to the homologous SA14 challenge. In addition survival range and median survival data indicated that pre-treatment with serum from individuals vaccinated with IXIARO* also delayed the onset of disease in affected animals.

As overall conclusion, these pharmacodynamic studies demonstrate that:

1. Antibodies are able to protect against JE infection i.e. protection is antibody based.
2. Antibodies generated against IXIARO* vaccination protect mice equally against lethal challenge with JEV SA14 and KE-093 (genotype III and genotype I respectively).
3. Protection against JEV correlates with the anti-JEV neutralizing antibody titre as measured by $PRNT_{50}$ assay.
4. A protective threshold for neutralizing antibodies of 1:10 is confirmed for the validated PRNT assay done at Intercell.
5. A PRNT titre of 1:10 is a reasonable cut-off for seroconversion.

TOXICOLOGY

Single dose and repeat dose toxicity studies, and local tolerance studies were not performed.

An extensive pre- and postnatal development study was performed with IXIARO* in rats which covered all stages of female reproduction.

Dosing was initiated with 6 mcg/0.5 mL IXIARO* either one or three weeks prior to mating, and continued every two weeks up to day 6 of gestation (i.e. either 2 or 3 intramuscular injections were administered in total). The rats were allowed to litter and followed together with the F1 generation for 21 days after birth for assessment of postnatal development and maternal behaviour.

Preliminary immunogenicity studies predicted that antibody levels would remain high up 42 days after the first injection. Therefore the animals were exposed both to the vaccine itself, as well as to antibodies generated against the vaccine, during the critical time periods likely to affect fertility, organogenesis, early to late embryo-foetal development, birth, maternal function, and also postnatal development. Furthermore, different levels of anti-JE virus antibodies were induced in the rats by two different IXIARO* treatment schedules prior to mating.

Table 40: Toxicology Studies Overview

Type of Study	Species	IXIARO* Lot Number	IXIARO* Route + Dose + Schedule
Pre- / post-natal developmental toxicity	Rat	ICB05/501	Two i.m. injections (day -7 before mating, day 6 after mating) or Three i.m. injections (day -21, day -7 before mating, day 6 after mating). 6 mcg/0.5mL of IXIARO* Neutralizing Ab titres by PRNT (day 21, 35, 49, 65)

There were no significant effects of treatment on the adult females (as measured by clinical signs, bodyweight or food consumption), or on the reproductive performance in terms of fertility, pregnancy outcome or post natal care. There were no effects on F1 neonatal pup weight, survival or development as assessed by the physical and functional tests applied.

The only statistically significant finding in this study was an increased incidence of incomplete ossification on skeletal examination of fetuses in the Vaccine II group at day 20 of gestation. The mean incidences per litter per group attained statistical significance ($p>0.05$) for incomplete ossification of 4 or more skull bones and ischia in the Vaccine II fetuses (where the adult females received 2 injections). Paradoxically, incomplete ossification in the Vaccine I group (where the animals received 3 injections) was essentially similar to the Controls.

The relevance of these findings for the use of the IXIARO* vaccine in humans was investigated further by considering historical control data on the strain of rats used in this study. The results from the control group used in this study were comparable to historical control data obtained in this strain of rats.

In the Vaccine II group, the only parameter that was statistically different from the control group was the incomplete *in utero* ossification in some regions (particularly pelvis and skull) noted in some gestation day 20 fetuses. There were no other indications of *in utero* growth delays and no indication of any postnatal growth retardation. If this truly represented a delay in *in utero* growth, it would be expected that other parameters measured would also reflect this. Since this observed delay in ossification occurred in isolation and was not corroborated by other evidence of delayed development (such as lower foetal weights corrected for litter size) and was without consequence (based on the extensive postnatal evaluations conducted in this study up to day 21 after birth), it was not considered to be an adverse effect. Furthermore, since it occurred in the group given just two injections and not in the group given three injections and in the group with the lower antibody titre at the beginning of gestation and a similar titre at the end of gestation (when ossification occurs), it seems unlikely that it can be attributed to treatment with the vaccine. Therefore, this isolated instance of more fetuses with incomplete ossification of some regions of the skeleton in the Vaccine II group (2 injections) was considered to be a spurious event and without relevance to the use of the vaccine in humans.

In the pre- and postnatal development toxicity study performed in rats either two or three doses of 6 mcg/0.5 mL IXIARO* were administered by intramuscular injection at two-week intervals. The dose, route of administration and the immunization schedule used in these

studies is comparable to the intended clinical use in humans of two intramuscular injections of 6 mcg / 0.5 mL given four weeks apart, which was used in the Phase 1, Phase 2 and Phase 3 clinical studies. This represents a very wide safety margin (i.e. a much higher dose in animals with respect to the human dose) in terms of dose per body weight and injection schedule.

In conclusion, the overall toxicology data demonstrate that IXIARO* is a safe and well tolerated vaccine. The findings concerning incomplete ossification in the pre- and postnatal development toxicity study could not be attributed to treatment with IXIARO* and were considered to be a spurious event although of unknown significance to the use of the vaccine in humans.

REFERENCES

1 Srivastava, A.K., Putnak, J.R., Lee, S. H., Hong, S.P., Moon, S.B., Barvir, D.A., Zhao, B., Olson, R.A., Kim, S., Yoo, W., Towle, A.C., Vaughn, D.W., Innis, B.L.,Eckels, K. H.. A purified inactivated Japanese encephalitis virus vaccine made in Vero cells. Vaccine 2001, 19:4557-4565

2 Hasegawa H, Yoshida M, Kobayashi Y, Fujita. Antigenic analysis of Japanese encephalitis viruses in Asia using monoclonal antibodies. Vaccine 1995, 13:1713-1721

3 Tauber E., Kollaritsch H., Korinek M., Rendi-Wagner P., Jilma B., Firbas C., Schranz S., Jong E., Klingler A., Dewasthaly S., Klade C.S. Safety and immunogenicity of a Vero-cell-derived, inactivated Japanese encephalitis vaccine: a non-inferiority, phase III, randomised controlled trial. Lancet 2007, 370:1-7.

4 Centers for Disease Control and Prevention. Inactivated Japanese encephalitis virus vaccine. Recommendations of the advisory committee on immunization practices (ACIP). MMWR 1993, 42:(No. RR- 1)

5 Tauber E, Kollaritsch H et al. Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial of the Safety and Tolerability of IC51, an Inactivated Japanese Encephalitis Vaccine. Journal of Infectious Diseases 2008; 198: 493-9

6 Schuller E, Jilma B et al. Long–term immunogenicity of the new Vero cell-derived, inactivated Japanese encephalitis virus vaccine IC51 Six and 12 month results of a multicenter follow-up phase 3 study. Vaccine 2008; 26: 4382-86

7 Kaltenböck A, Dubischar-Kastner K et al. Safety and immunogenicity of concomitant vaccination with the cell-culture based Japanese Encephalitis vaccine IC51 and the hepatitis A vaccine HAVRIX1440 in healthy subjects: A single-blind, randomized, controlled Phase 3 study. Vaccine 2009; 27: 4483-4489

8 Hombach J, Solomon T et al. Report on a WHO consultation on immunological endpoints for evaluation of new Japanese encephalitis vaccines, WHO, Geneva, 2-3 September, 2004. Vaccine 2005; 23: 5205-5211.

9 Schuller E, Klade CS et al. Comparison of a single, high-dose vaccination regimen to the standard regimen for the investigational Japanese encephalitis vaccine, IC51: A randomized, observer-blind, controlled Phase 3 study. Vaccine 2009; 27: 2188-2193

10 Kaltenböck A, Dubischar-Kastner K et al. Immunogenicity and safety of IXIARO* (IC51) in a Phase II study in healthy Indian children between 1 and 3 years of age. Vaccine 2010; 28: 834-839

11 Dubischar-Kastner K, Eder S et al. Long Term Immunity and Immune Response to a Booster Dose Following Vaccination with the Inactivated Japanese Encephalitis Vaccine IXIARO* , IC51.
Vaccine 2010; 28: 5197-5202

12 Dubischar-Kastner K, Kaltenböck A et al. Safety Analysis of a Vero-cell Culture Derived Japanese Encephalitis Vaccine, IXIARO* (IC51), in 6 Months of Follow-up. Vaccine 2010, 28: 6463-6469

13 Eder S, Dubischar-Kastner K et al. Long Term Immunity Following a Booster Dose of the Inactivated Japanese Encephalitis Vaccine IXIARO*, IC51.Vaccine 2011, 29: 2607-12

PART III: CONSUMER INFORMATION

IXIARO*
Japanese encephalitis vaccine (inactivated, adsorbed)

This leaflet is part III of a three-part "Product Monograph" published when IXIARO* was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about IXIARO*. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
IXIARO* is a vaccine against the virus which causes Japanese encephalitis (encephalitis – is infection of the brain).
Japanese encephalitis is caused by the Japanese encephalitis virus that is found across Asia, including many tourist destinations, as well as in northern Australia. The virus is transmitted to humans by the bite of infected mosquitoes.

What it does:
IXIARO* is used for vaccination (active immunization) against Japanese encephalitis virus in persons 18 years of age and older,

- who plan to reside in or travel to areas where Japanese encephalitis is common (endemic) or seasonal (epidemic) particularly during the transmission season. Depending on your outdoor activities in rural areas your doctor will explain your individual risk of catching the disease.
- who work with Japanese encephalitis virus both in laboratories as well as in industry.

When it should not be used:
IXIARO* is not recommended for use in persons below 18 years of age.
Individuals with the following conditions should discuss vaccination with their physician, who will be able to advise on safe vaccination or alternative preventative measures to avoid infection with JEV:

- Pregnant or breast feeding women
- Persons with bleeding disorder, or abnormal bruising
- Persons with fever (temperature above 37.8°C)
- Immunosuppressed persons or individuals on cancer treatment

What the medicinal ingredient is:
A single dose (0.5-mL of sterile suspension) of IXIARO* contains:
6 micrograms (protein content) of inactivated Japanese encephalitis virus (attenuated strain SA_{14}-14-2 produced in Vero cells) adsorbed on aluminum hydroxide, hydrated (0.25 mg Al/dose).

What the important nonmedicinal ingredients are:
Disodium hydrogen phosphate
Potassium dihydrogen phosphate
Sodium chloride
Water for injection

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

What dosage forms it comes in:
Suspension for injection, 6 mcg protein/dose

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

- IXIARO* must never be injected into a vein or any blood vessel.
- As with any other vaccine, vaccination with IXIARO* may not result in protection in all cases.
- IXIARO* will not protect against encephalitis caused by other organisms.
- Like other intramuscular injections, this vaccine should not be administered intramuscularly to persons with thrombocytopenia, hemophilia or other bleeding disorders.
- If your immune system does not work properly (immunodeficiency) or you are taking medicines affecting your immune system (such as a medicine called cortisone or cancer medicine), protection may not be as expected.

BEFORE you use IXIARO* talk to your doctor or pharmacist if:

- you have a bleeding disorder (a disease that makes you bleed more than normal) or a reduction in blood platelets, which increases risk of bleeding or bruising (thrombocytopenia).
- you are or think you are pregnant or if you are breast feeding.
- you have any known allergies.

INTERACTIONS WITH THIS MEDICATION

A study in humans to evaluate the effectiveness and safety of medicines (clinical trial) has shown that IXIARO* can be given at the same time with HAVRIX. Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription or have recently received any other vaccine.

PROPER USE OF THIS MEDICATION

Usual dose:
The primary vaccination series consists of two doses of 0.5 mL each according to the following schedule:
First dose: Day 0
Second dose: 28 days after first dose

Overdose:
No case of overdose has been reported.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
Make sure you finish the complete vaccination course of two injections. If not, you may not be fully protected against the disease. If you miss a scheduled injection, talk to your doctor and arrange another visit for the second injection.
There is data that the second injection can be given up to 11 months after the first one.

Booster Dose
A booster dose can be given within the second year (i.e. 12-24 months) after the first dose of the recommended primary immunization. Your doctor will decide on requirement of booster.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, IXIARO* can cause side effects, although not everybody gets them.

Anaphylactic shock is a rare but very serious event. An allergic reaction causes symptoms in many parts of the body, often starting with tingling or swelling around the mouth and lips. The face and neck may swell and breathing may become difficult. Heartbeat is fast and may be irregular. A rash, hives or redness of the skin may occur and there may be diarrhea. If these symptoms occur, contact your physician or call your emergency services immediately.

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

Very common (in one or more than 1 in 10 of those who are vaccinated):
Headache, muscle pain, injection site reactions (pain, tenderness)

Common (in one or more than 1 in 100 of those who are vaccinated):
Nausea, influenza like illness, fever, tiredness, injection site reactions (redness, hardening, swelling, itching)

Uncommon (in one or more than 1 in 1,000):
Vomiting, skin rash, changes in lymph nodes, migraine (throbbing headache, often accompanied by nausea and vomiting and sensitivity to light), dizziness, vertigo (spinning sensation), diarrhoea, belly pain, itching, chills, general condition of feeling unwell, musculoskeletal stiffness, runny or blocked nose, inflammation of nose and throat, injection site reactions (bleeding, bruising), abnormal laboratory liver test results

Rare (in one or more than 1 in 10,000):
Platelet deficiency, nerve inflammation, foot, leg and ankle swelling, palpitations, rapid heartbeat, difficulty to breathe, abnormal sensation of skin, hives, pain in leg or arm, joint pain, skin redness

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

HOW TO STORE IT

Keep out of the reach and sight of children.
Do not use IXIARO* after the expiry date which is stated on the carton and label after "EXP". The expiry date refers to the last day of that month.
Store in a refrigerator (2°C - 8°C).
Do not freeze. If the vaccine has been frozen it should not be used.
Store in the original package in order to protect from light

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects case reports on adverse events following immunization.

For health care professionals:
If a patient experiences an adverse event following immunization, please complete the appropriate Adverse Events following Immunization (AEFI) Form and send it to your local Health Unit in ***your province/territory****.*

For the General Public:
Should you experience an adverse event following immunization, please ask your doctor, nurse, or pharmacist to complete the Adverse Events following Immunization (AEFI) Form.
If you have any questions or have difficulties contacting your local health unit, please contact Vaccine Safety Section at Public Health Agency of Canada

By toll-free telephone: 866-844-0081
By toll free fax: 866-844-5931
Email: caefi@phac-aspc.gc.ca
Web: http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php
Mail:
The Public Health Agency of Canada
Vaccine Safety Section
130 Colonnade Road, A/L 6502A
Ottawa, ON K1A oK9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www. novartis.ca
or by contacting Novartis Pharmaceutical Canada Inc. at:
1-800-363-8883

This leaflet was prepared by Valneva

Last revised: 1 October 2013