Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

To:	Scott Proestel, MD Director, Division of Epidemiology (DE) Office of Biostatistics and Epidemiology (OBE)
Through:	Craig Zinderman, MD, MPH Associate Director for Product Safety, DE, OBE
From:	Meghna Alimchandani, MD Chief, Pharmacovigilance Branch, DE, OBE
Subject:	Pediatric Safety and Utilization Review for the Pediatric Advisory Committee (PAC) Meeting
Product:	Ixiaro (Japanese Encephalitis Vaccine, Inactivated, Adsorbed)
Sponsor:	Valneva Austria GmbH/Intercell
STN:	BLA 125280/208
Indication:	Ixiaro is indicated for active immunization for the prevention of disease caused by Japanese encephalitis virus (JEV) and is approved for use in individuals 2 months of age and older.
PAC Meeting Date:	September 14, 2016

1. INTRODUCTION

1.1 Product Description

Ixiaro (Japanese Encephalitis Vaccine, Inactivated) marketed by Valneva Austria GmbH is indicated for active immunization for the prevention of disease caused by Japanese encephalitis virus (JEV) in individuals 2 months of age and older. This vaccine is supplied as a sterile suspension in 0.5 mL single dose pre-filled syringes. Ixiaro is administered as a two-dose series, with 28 days between doses. Additionally, if ongoing exposure/re-exposure to JEV is expected, a booster dose may be given in individuals ≥ 17 years.

Table 1: Adapted from Ixiaro US Package Insert (updated May 2014)
Highlights of Prescribing Information (Dosage and Administration)

Age	Dose*	Primary Series
Children 2 months to < 3 years of age	0.25 mL	2 doses, 28 days apart
Individuals 3 years of age and older	0.5 mL	2 doses, 28 days apart

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

1.2 Regulatory History

Ixiaro was approved in the US on March 30, 2009, which is also its international birthdate. Currently, Ixiaro is licensed in Australia, New Zealand, Europe, Canada, Switzerland, Hong Kong, Singapore and Israel. The May 17, 2013, approval to expand its use to include individuals 2 months to <17 years is the trigger for this Pediatric Safety and Utilization Review for the Pediatric Advisory Committee (PAC). Key dates in its regulatory history are described in Table 2.

Table 2: Ixiaro Regulatory History

March 30, 2009	Initial US approval of Ixiaro for use in individuals ≥ 17 years
October 14, 2010	FDA approved revisions to the package insert to include long-term immunogenicity data and use of a booster dose in individuals ≥ 17years
September 25, 2012	Ixiaro was granted Orphan Drug status for use in individuals 2 months to <17 years of age, based on anticipated use in fewer than 200,000 individuals in this age range annually in the US
May 17, 2013 **(PAC trigger)**	FDA approved expansion of use to include individuals 2mo to <17y

2. OBJECTIVES AND SCOPE

The objective of this memorandum for the Pediatric Advisory Committee (PAC) is to present a comprehensive review of the postmarketing pediatric safety following approval for expanded age usage in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. The trigger for this pediatric postmarketing safety review is the May 17, 2013, approval of Ixiaro for expanded age usage in individuals 2 months to <17years. This review covers the period from May 17, 2013, through December 31, 2015.

An abbreviated presentation of this review to the PAC is planned for this product as it does not meet the criteria that would necessitate a full oral presentation or a justified abbreviated presentation. Specifically, no new significant safety signals have been identified and no pediatric deaths were reported in the review period. Ixiaro does not have a requirement for a safety postmarketing study (PMR) or Risk Evaluation and Mitigation Strategy (REMS). There have been no safety-related label changes to the US package insert during the review period. Although the PAC presentation is abbreviated, the analysis of the safety data is comprehensive, and this memorandum documents FDA's complete evaluation, including review of adverse event reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature.

3. MATERIALS REVIEWED

3.1 Vaccine Adverse Events Reporting System (VAERS)

- VAERS reports for Ixiaro submitted May 17, 2013 – December 31, 2015
- VAERS reports for Ixiaro submitted March 30, 2009 – December 31, 2015

3.2 Manufacturer's Submissions

- Product Distribution Data, dated May 20, 2016
- Ixiaro Pharmacovigilance Plan Version 3.0, dated June 11, 2012
- Ixiaro Periodic Safety Update Reports (PSURs)
  - Reporting period April 1, 2013 – March 31, 2014
  - Reporting period April 1, 2014 – March 31, 2015
  - Reporting period April 1, 2015 – March 31, 2016
- Ixiaro Package Insert (updated May2014)

3.3 FDA Documents

- Ixiaro Approval Letter, dated March 30, 2009
- Ixiaro Approval Letter, dated October 14, 2010
- Ixiaro Approval Letter, dated May 17, 2013
- Summary Basis for Regulatory Action, dated May 16, 2013

3.4 Publications (see section 8)

4. LABEL CHANGES IN REVIEW PERIOD

There were no safety-related label changes to the US package insert during the review period.

5. PRODUCT UTILIZATION DATA

US data during PAC review period: According to Valneva, 605, 208 doses of Ixiaro were distributed in the US from May 1, 2013, to December 31, 2015. Since Ixiaro is administered as a two-dose series, patient exposure may be estimated to be 302, 604 individuals in the US. (Please note that the number of doses distributed is an estimate of the number of patients vaccinated because doses may have been distributed without being administered to patients or patients may have received additional doses.) Pediatric-specific utilization data are not available. However, Valneva states that "*all non-quantitative sources (CDC survey of travelers to Asia, etc.) clearly indicate that the vast majority of Ixiaro usage is in adults.*"

Worldwide data during PAC review period: During May 17, 2013, to December 31, 2015, 1,520,049 doses were distributed or released worldwide. Valneva uses marketing partners to

distribute Ixiaro in certain non-US countries, and notes that not all doses released by Valneva may have been actually distributed in these countries.

US data during historical review period: During March 30, 2009 (initial US licensure) to December 31, 2015, Valneva distributed 998,857 doses of Ixiaro in the US.

Worldwide data during historical review period: During March 30, 2009 (initial US licensure) to December 31, 2015, Valneva distributed or released 3,326,304 doses of Ixiaro worldwide.

6. PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

Safety concerns for Ixiaro as per the sponsor's most recent pharmacovigilance plan (PVP) are described in Table 3 (Version 3.0, dated June 11, 2012). The PVP includes the manufacturer's assessment of identified and potential risks based on pre-licensure clinical trials, postmarketing safety monitoring, published literature, and known product-class effects.

Table 3: Summary of safety concerns for Ixiaro

[Source: Intercell Risk Management Plan, Ixiaro, Version 3.0, 11 June 2012, p. 33]

Important identified risks	**Sensitivity or allergic reactions** Dermatitis (dermatitis allergic, dermatitis) Dyspnoea (dyspnoea) Erythema (erythema) Eye pruritus (eye pruritus) Flushing (hot flush, flushing) Hypersensitivity (hypersensitivity, drug hypersensitivity) Pruritus (pruritus, pruritus generalised) Rash (rash, rash maculo-papular, rash pustular, rash macular, rash pruritic, rash erythematous) Urticaria (urticaria localized, urticaria) **Neurological adverse events** Convulsion
Important potential risks	**Sensitivity or allergic reactions** MedDRA PTs: Conjunctivitis (conjunctivitis allergic) Hypotension (hypotension) **Neurological adverse events** Acute disseminated encephalomyelitis Acute Encephalitis Acute Myelitis Central Nervous System Inflammation Guillain-Barré-Syndrome
Important missing information	There are limited data regarding vaccination with IXIARO® during pregnancy and lactation. Information on immuno-suppressed persons is missing or limited, as is information on co-vaccinated individuals.

No safety signals were identified in the premarket pediatric clinical safety database and adverse reactions were generally mild and transient. "The most common risks associated with Ixiaro in infants and children 2 months to <3 years of age are erythema at the injection site, fever, irritability, and diarrhea. The most common risks associated with Ixiaro in children and adolescents 3 to <18 years of age are pain and tenderness at the injection site, muscle pain, and fatigue[1]."

Primary immunization with Ixiaro in children 2 months to <3 years of age consists of two 0.25 mL doses, administered 28 days apart. The package insert section on Dosage states: "To administer a 0.25 mL dose, expel and discard half of the volume from the 0.5 mL pre-filled syringe by pushing the plunger stopper up to the edge of the red line on the syringe barrel prior to injection[2]." Upon approval of use in this age range, the Summary Basis for Regulatory Action (SBRA) noted that "variability in the prepared dose may arise from human factors issues related to comprehension and execution of the preparation instructions[3]." The SBRA also noted that available premarket safety data in children 1 to <3 years of age who received two 0.5mL doses suggested low likelihood of increased reactogenicity, and it was concluded that there was a "low risk of doses in excess of the intended 0.25 mL dose to infants and children 2 months to <3 years." Additionally, the sponsor agreed to a postmarketing commitment study to assess human factors issues for the 0.25 mL dose preparation method.

The sponsor's planned pharmacovigilance activities for Ixiaro include passive and active surveillance, as described below. The sponsor plans to evaluate neurologic AEs and hypersensitivity/allergic reactions through routine surveillance and postmarketing studies.

6.1 Routine surveillance

The sponsor conducts AE reporting in accordance with 21 CFR 600.80.
The PVP also includes plans to administer a questionnaire to women vaccinated during pregnancy to ensure consistent data capture and to conduct follow-up until 3 months after delivery or termination of the pregnancy. Potential risks and complications will be followed up until resolution or until no further information is expected.

6.2 Postmarketing studies

Completed safety postmarketing studies related to pediatrics:

1. IC51-325 – Long term immunogenicity and safety with or without a booster dose following primary vaccination with Ixiaro in a pediatric population in JEV-endemic countries. This study was required under the Pediatric Research Equity Act (PREA) to evaluate the safety and immunogenicity of Ixiaro in individuals < 17 years of age. There were no new safety concerns.
2. Study to conduct postmarketing assessments of human factors issues that may affect preparation and administration of the 0.25mL dose in children 2 months to < 3 years of age. The sponsor agreed to conduct this study as a postmarketing commitment upon the

[1] Summary Basis for Regulatory Action dated May 16, 2013; STN 125280/125
[2] Ixiaro US Package Insert (updated May2014)
[3] Summary Basis for Regulatory Action dated May 16, 2013; STN 125280/125

2013 approval for use in individuals 2 months to < 17 years of age. This study has been completed and the results are under review by FDA.

Pending safety postmarketing studies:

3. Study IC51-401 – Active surveillance for adverse events in 20,000 US military personnel.
4. Study IC51-401 – Electronic surveillance of pregnancy cases in those 20,000 personnel.
   Overview of IC51-401 studies: These studies are being performed in collaboration with the U.S. Department of Defense (DoD) Military Vaccine (MILVAX) Agency, using the Defense Medical Surveillance System (DMSS) database and the DoD electronic health record. The sponsor agreed to conduct both IC51-401 studies as postmarketing commitments upon initial approval of Ixiaro in 2009. Pre-selected adverse events occurring within 42 days of vaccination with Ixiaro will be identified using ICD-9-CM coded data obtained from the DMSS records of 20,000 vaccinated military personnel. A data mining analysis will be used to identify other AEs that occur frequently in the time period following Ixiaro vaccination.
   Primary objective of the study is to investigate potential rare serious adverse events (SAEs) such as neurological or hypersensitivity reactions.
   Secondary objective of the study is to investigate pregnancy and infant health outcomes for up to 3 months after delivery among females vaccinated with Ixiaro.
   Current status: The study was started in 2011 and is ongoing.

To date, there have been no postmarketing signals for the safety concerns described in Table 3.

7. SPONTANEOUS ADVERSE EVENT (AE) REVIEW

7.1 Methods

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event (AE) reports following Ixiaro use during the PAC review period from May 17, 2013 (approval of pediatric age indication) to December 31, 2015. All serious AE (SAE) reports in the pediatric age group and all death reports were individually reviewed. VAERS was also queried for AEs following Ixiaro use from March 30, 2009 (initial approval) to December 31, 2015, to assess the historical frequency and nature of AE reporting for Ixiaro prior to the May 17, 2013, approval for use in individuals ≥ 2 months old.

Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, variable report quality and accuracy, inadequate/missing data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups.

7.2 Results

During the PAC review period from May 17, 2013 (approval of pediatric age indication) to December 31, 2015, VAERS received 124 reports of AEs following use of Ixiaro (Table 4). There were 3 serious and 5 non-serious reports in individuals <18 years of age. There were no pediatric deaths. The majority of reports are for non-serious AEs in adults.

Table 4: Ixiaro VAERS reports during PAC review period 5/17/13 (pediatric age indication) – 12/31/15

Age	*Serious Non-Fatal			Deaths			Non-Serious			Total		
	US	Foreign	Total	US	Foreign	Total	US	Foreign	Total	US	Foreign	Total
< 18 years	3	0	3	0	0	0	5	0	5	8	0	8
≥ 18 years	9	24	33	1	0	1	75	0	75	85	24	109
Unknown	0	7	7	0	0	0	0	0	0	0	7	7
All Ages	12	31	43	1	0	1	80	0	80	93	31	124

*Serious non-fatal AEs include Otherwise Medically Important Conditions (OMIC), life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, or significant disability.

7.2.1 Deaths

During the review period there were no reports of pediatric deaths following vaccination with Ixiaro. There was one adult death in the review period; described below. The death was not attributed to Ixiaro.

- Sudden death of a 42-year-old male who "collapsed while running." The time between vaccination and onset of symptoms is not known. An autopsy was performed which determined the final cause of death to be "Sudden Cardiac Death Due to Ischemic Heart Disease." Autopsy findings included "healed myocardial infarct of anteromedial left ventricular wall, occlusive coronary atherosclerosis, left ventricular hypertrophy."

7.2.2 Non-fatal serious adverse event reports (SAEs)

During the review period, there were 43 non-fatal SAE reports, only 3 of which involved individuals <18 years of age. The 3 pediatric SAE reports included one duplicate report, thus yielding only 2 serious pediatric cases.

- New-onset seizures in a 15-year-old male who received concomitant vaccination with Ixiaro, Rabavert, Typhim Vi and YF-Vax. He experienced a partial seizure "1 week after 1st round of travel vaccines" and "grand mal seizure 1 week after last round of travel vaccines." He is also reported to have been suffering from headaches, "feeling unwell, vomited." Laboratory work up, imaging, and EEG did not reveal any abnormalities. Reviewer comment: Possible infectious etiology (patient is reported to have been "unwell" and experienced vomiting), or other etiology of seizures needs further evaluation. This case is also confounded by multiple concomitant vaccines. New onset of seizures can have multiple possible etiologies including infection. There is not sufficient evidence to attribute the cause of this patient's seizures to the vaccine versus another etiology.
- 15-year-old female with history of depression and anxiety, received concomitant vaccination with Ixiaro and rabies vaccine. Four days post-vaccination, she developed cervical and supraclavicular lymphadenopathy. She was later diagnosed with "inflammatory thyroiditis"; symptoms resolved without treatment.

7.2.3 Non-serious adverse event reports (AEs)

During the review period, there were 80 non-serious AE reports, only 5 of which involved individuals <18 years of age. In the pediatric group, the only MedDRA PT reported in >1 case was for malaise (n = 2).

7.2.4 Historical VAERS Data: 3/30/09 (initial approval) – 12/31/15

Table 5 summarizes the 253 Ixiaro AE reports submitted to VAERS during the 6.5 year historical review period from March 30, 2009 (initial approval) to December 31, 2015, overall and by age.

Table 5: Ixiaro VAERS reports during historical review period 3/30/09 (initial approval) – 12/31/15

Age	*Serious Non-Fatal			Deaths			Non-Serious			Total		
	US	Foreign	Total	US	Foreign	Total	US	Foreign	Total	US	Foreign	Total
< 18 years	3	0	3	0	0	0	7	0	7	10	0	10
≥ 18 years	34	51	85	1	1	2	143	1	144	178	53	231
Unknown	2	9	11	0	0	0	1	0	1	3	9	12
All Ages	39	60	99	1	1	2	151	1	152	191	62	253

*Serious non-fatal AEs include Otherwise Medically Important Conditions (OMIC), life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, or significant disability.

There were 10 pediatric reports, which included 3 serious (non-fatal) and 7 non-serious reports in individuals <18 years. There were no additional pediatric SAE reports or pediatric deaths in the historical review period (the 3 pediatric SAE reports were previously described in section 7.2.2). There were 2 adult deaths since licensure; one case has been previously described in section 7.2.1 and the second case is described below; neither case was attributed to Ixiaro.

- Death of a 26-year-old female (b) (6) months post-vaccination with Ixiaro. The patient received concomitant vaccinations with Ixiaro, yellow fever and rabies vaccines, as well as other unspecified "pre-travel vaccinations" and doxycycline for malaria prophylaxis prior to a "year long backpacking journey." The second dose of Ixiaro was administered on 12/6/11 (14 days after the first dose rather than the recommended 28 days for primary vaccination with Ixiaro). The VAERS report states that during her travels in foreign countries, she developed influenza-like symptoms, fever, dizziness, and had difficulty speaking. She had to be "airlifted to a hospital" and was diagnosed with viral encephalitis (not specified further) with associated brain damage. She died approximately one week after onset of symptoms on (b) (6)

  Reviewer comment: The rapidly deteriorating clinical course and symptoms are consistent with an infectious etiology. This case is also confounded by multiple concomitant vaccines. Vaccine failure of Ixiaro is a possibility, although the pathogen was not identified in this case. Ixiaro package insert, section 5.2 states: "Limitations of Vaccine Effectiveness: Vaccination with IXIARO may not protect all individuals."

Thus, no substantive differences were observed between the historical period and the recent review period (5/17/13 – 12/31/15) with respect to the types and frequencies of adverse events.

7.3 Data Mining

Data mining was conducted using Empirica Signal software (version 7.2) to evaluate whether any AEs following use of Ixiaro were disproportionally reported when compared to adverse event reporting for other vaccines in the VAERS database. The background database contains VAERS reports since 1990. Data mining findings are subject to a number of potential

limitations and do not imply causality. Alerts of disproportional adverse event reporting do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation.

No disproportional reporting alerts with EB05 (the lower bound of 95% confidence interval of empirical Bayesian geometric mean) greater than 2 were identified for Ixiaro. (Data mining query was performed on April 14, 2016 with data through September 2, 2015).

7.4 Periodic Safety Reports

The sponsor's postmarketing periodic safety reports for Ixiaro during the PAC reporting period were reviewed and there were no new safety concerns identified for Ixiaro, and no actions were taken for safety reasons.

In the Periodic Safety Update Report (PSUR) for reporting interval April 1, 2014 – March 31, 2015, the sponsor noted that in their EU Risk Management Plan (version 6.0, dated 1/26/2015), they are now considering the previously important *identified* risk of "convulsion" (referring to non-febrile convulsion) to be an important *potential* risk, noting that evaluation of available data (including postmarketing data) did not identify convulsion as a safety signal following Ixiaro use, and that there is no confirmed pathophysiological pathway to support a vaccine induced etiology. The sponsor will continue to monitor convulsion as an important potential risk for Ixiaro. The sponsor also notes that "*convulsion is still considered a safety concern, is reflected in the RMP [Risk Management Plan] and PSUR as such, and will have the same level of PV scrutiny as applied before*." The sponsor also added two new important *potential* risks of "febrile convulsion" and "accidental overdose" to the EU Risk Management Plan (version 6.0, dated 1/26/2015). Febrile convulsion was included in context of the pediatric indication and etiology of febrile convulsions in children. Accidental overdose was included in the context of a new rapid vaccination schedule that was approved in April 2015 in Europe. According to the sponsor, accidental overdose may occur in the accelerated regimen.

8. LITERATURE REVIEW

A search of the US National Library of Medicine's PubMed.gov database on 5/11/16 for peer-reviewed literature published between May 17, 2013, and December 31, 2015 with filters (Human, English) and search term "Ixiaro" yielded 8 publications. Abstracts and articles were reviewed for relevant safety information, summarized in the table below. No articles were published during the review period that would suggest new safety concerns for Ixiaro.

Article	Safety Conclusion
Erra EO, Kantele A. The Vero cell-derived, inactivated, SA14-14-2 strain-based vaccine (Ixiaro) for prevention of Japanese encephalitis. Expert Rev Vaccines. 2015; 14(9):1167-79. Review.	The authors conclude that Ixiaro "appears well-tolerated, with no alarming safety concerns detected" and that "continuing surveillance for potential rare adverse events is vital as experience with the vaccine accumulates."
Paulke-Korinek et al. Persistence of antibodies six years after booster vaccination with inactivated vaccine against Japanese encephalitis. Vaccine. 2015 Jul 9;33(30):3600-4.	The study demonstrated long-term protection and persistence of antibodies 6 years after booster vaccination with Ixiaro in 67 subjects. Authors recommend additional booster doses 10 years

	following the first booster dose.
Jelinek et al. Evaluation of rabies immunogenicity and tolerability following a purified chick embryo cell rabies vaccine administered concomitantly with a Japanese encephalitis vaccine. Travel Med Infect Dis. 2015 May-Jun; 13(3):241-50.	Study investigated accelerated (1 week) regimen of concomitant vaccination with Ixiaro and Rabipur. Local and systemic adverse AEs were comparable across different regimens. All AEs resolved and there were no deaths in the study. The authors concluded that "*An accelerated pre-exposure rabies and JE vaccination regimen is non-inferior to the standard four-week rabies regimen and may thus provide a more convenient regimen for individuals traveling to endemic countries at short notice*."
Firbas C, Jilma B. Product review on the JE vaccine IXIARO. Hum Vaccin Immunother. 2015;11(2):411-20. Review.	The authors state that "the safety, tolerability and immunogenicity profile of IXIARO® is well established through a number of clinical studies." The authors conclude that "As vaccination is the most feasible, reliable and cost effective tool for JE control, IXIARO® with confirmed excellent safety profile is highly recommendable, in particular for vaccination of children at risk. The European Commission as well as the FDA approved the extension of indication of IXIARO® to the pediatric segment (2 months of age and older)."
Rabe et al. Adverse events following vaccination with an inactivated, Vero cell culture-derived Japanese encephalitis vaccine in the United States, 2009-2012. Vaccine. 2015 Jan 29;33(5):708-12.	Authors reviewed 42 adverse event reports submitted to VAERS involving adults who received Ixiaro from May 2009 through April 2012. Only 5 reports were classified as serious AEs, for a reporting rate of 1.8 per 100,000 doses. There were no deaths. Hypersensitivity reactions (N = 12) were the most common type of AEs reported; there were no cases of anaphylaxis. The postmarketing data are reassuring and support the good safety profile of Ixiaro.
Use of Japanese encephalitis vaccine in children: recommendations of the advisory committee on immunization practices, 2013. MMWR Morb Mortal Wkly Rep. 2013 Nov 15;62(45):898-900.	Following FDA approval of the pediatric indication, the ACIP voted to extend recommendations for use of Ixiaro to include children 2 months through 16 years.
Erra et al. Cross-protection elicited by primary and booster vaccinations against Japanese encephalitis: a two-year follow-up study. Vaccine. 2013 Dec 17; 32(1):119-23.	Ixiaro has largely replaced older Japanese Encephalitis virus (JEV) vaccines developed from mouse brain-derived preparations (JE-MB). The study shows that Ixiaro can be used to boost immunity in JE-MB-primed vaccinees. Ixiaro thus provides cross-protective immunity against non-

	vaccine JEV genotypes.
Jelinek T. IXIARO updated: overview of clinical trials and developments with the inactivated vaccine against Japanese encephalitis. Expert Rev Vaccines. 2013 Aug;12(8):859-69.	The author concludes that "Postmarketing studies have confirmed the excellent safety profile" and recommends that "since a safe and effective vaccine against Japanese encephalitis is now available, outdated guidelines and recommendations have to be revised: travelers to rural areas of Asia should generally be recommended vaccination."

9. CONCLUSION

No new safety signals were identified for Ixiaro from the postmarketing pediatric safety review of passive surveillance adverse event reports, sponsor's periodic safety reports and published literature. In general, very few adverse events were reported in the pediatric age group (<18 years) during the review period, compared to the number of individuals expected to have received the vaccine based on dose distribution data. There were no reports of pediatric death following use of Ixiaro, and no unusual frequency, clusters, or other trends for adverse events were identified that would suggest a new safety concern.

10. RECOMMENDATIONS

FDA recommends continued routine surveillance of Ixiaro. Final study reports of postmarketing studies will be reviewed when available. No further regulatory action is indicated at this time.