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

MEMORANDUM

To:	Craig Zinderman, MD, MPH Associate Director for Medical Policy Office of Biostatistics and Pharmacovigilance (OBPV) Center for Biologics Evaluation and Research (CBER)
From:	Meghna Alimchandani, MD Deputy Director, DPV, OBPV, CBER
Subject:	Safety and Utilization Review for the Pediatric Advisory Committee
Applicant:	Valneva Austria GmbH
Product:	Ixiaro (Japanese Encephalitis Vaccine, Inactivated, Adsorbed)
STN:	125280/368
Indication:	Ixiaro is a vaccine indicated for the prevention of disease caused by Japanese encephalitis virus (JEV). Ixiaro is approved for use in individuals 2 months of age and older.
Meeting Date:	Pediatric Advisory Committee Meeting, September 2023

Contents

1 INTRODUCTION

1.1 Objective

This memorandum for the Pediatric Advisory Committee (PAC) presents a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the approval 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 was the approval of the supplemental Biologics License Application (sBLA) 125280/235 on April 13, 2018, for use of Ixiaro booster dose in individuals 2 months to <17 years of age who are at risk of continued exposure or re-exposure to Japanese encephalitis virus.

This memorandum documents the Food and Drug Administration's (FDA's) complete evaluation, including review of adverse event (AE) reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature.

1.2 Indication and Product Description

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

This vaccine is supplied as a sterile suspension in 0.5 mL single dose pre-filled syringes for intramuscular administration. The primary series is administered as a two-dose series, with 28 days between doses. A booster dose (third dose) may be given at least 11 months after completion of the primary immunization series if ongoing exposure or re-exposure to JEV is expected.

1.3 Regulatory History

- March 30, 2009: Initial approval of BL 125280/0 for use in individuals ≥17 years
- October 14, 2010: Approval of BL 125280/19 to include long term immunogenicity data in the package insert and the 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: Approval of BL 125280/125 for use in individuals 2 months to <17years of age. [This approval was the *trigger for a previous PAC utilization and safety review (BL 125280/208*), prepared for September 14, 2016 PAC meeting.]
- April 13, 2018: Approval of BL 125280/235 for use of Ixiaro booster dose in individuals 2 months to <17 years of age
    - Trigger for current PAC review

- October 4, 2018: Approval of BL 125280/251 to include an alternate primary immunization series of two 0.5 mL doses of Ixiaro administered at 7 days apart for individuals 18 through 65 years of age, and ii) update the Ixiaro package insert to include data to support the concomitant use of Ixiaro primary immunization series, two 0.5 mL doses administered 28 days apart, with U.S.-licensed rabies vaccine (RabAvert) administered for pre-exposure prophylaxis.

2 MATERIALS REVIEWED

- Vaccine Adverse Events Reporting System (VAERS)
  - VAERS reports for Ixiaro during April 13, 2018, to May 31, 2023 (safety review period)
- Manufacturer's Submissions
  - Ixiaro U.S. package insert; updated September 2018
  - Applicant response to information request regarding dose distribution data, received July 18, 2023
  - Pharmacovigilance Plan, Version 6.0, dated January 26, 2015
  - Periodic safety reports
- FDA Documents
  - BL 125280/235 approval letter dated April 13, 2018
  - BL 125280/235 Pharmacovigilance Plan Review Memorandum
- Publications (see Literature Search in Section 7)

3 LABEL CHANGES IN REVIEW PERIOD

There were no safety-related label changes to the US package insert (USPI) between April 13, 2018 to May 31, 2023.

4 PRODUCT UTILIZATION DATA

Valneva Austria GmbH provided estimates of Ixiaro distribution data for the U.S. and worldwide for the safety review period (April 13, 2018, to May 31, 2023):

- U.S.: (b) (4) doses distributed
- Worldwide: (b) (4) doses distributed

The sponsor also provided the following estimated number of individuals vaccinated:

- U.S.: (b) (4) vaccinees
- Worldwide: (b) (4) vaccinees

The sponsor was not able to provide data on proportion of doses distributed to pediatric and adult patients. Note that the number of doses distributed is an estimate of the number of individuals vaccinated and based on assumptions regarding the number of individuals that received 1, 2 or 3 doses.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan

The manufacturer's current Pharmacovigilance Plan (PVP), Version 6.0, dated January 26, 2015, lists the following important potential risks, and missing information for Ixiaro (see Table 1). There are no important identified risks in the PVP.

Table 1: Ixiaro Safety Concerns

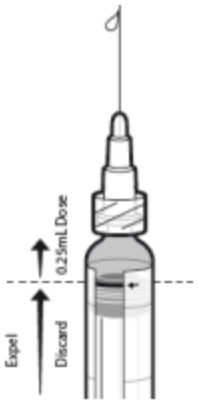
Important Potential Risks
Accidental overdose
Acute disseminated encephalomyelitis
Acute encephalitis
Acute myelitis
Central nervous system inflammation
Convulsion
Febrile convulsion
Guillain-Barré-Syndrome
Meningitis
Missing Information
There are limited data regarding vaccination with Ixiaro during pregnancy and lactation
Information on immunosuppressed persons is missing or limited.

Accidental overdose may occur if the product is administered incorrectly. Ixiaro is supplied as a sterile suspension in 0.5 mL single dose pre-filled syringes. The USPI includes a section on "Preparation of a 0.25 mL Dose of IXIARO for Administration to Children 2 Months to <3 Years" (section 2.3 of USPI). To administer a 0.25 mL dose, the label provides instructions to 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.

Age	Dose*	Primary Series
Children 2 months to <3 years of age	0.25 mL	2 doses, 28 days apart
Children and adolescents 3 to <18 years of age	0.5 mL	2 doses, 28 days apart
Adults 18 through65 years of age	0.5mL	2 doses, 7 days apart or 2 doses, 28 days apart
Adults older than 65 years of age	0.5mL	2 doses, 28 days apart

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

Figure 1:
Preparation for Administration of 0.25 mL Dose



A human factors study is being conducted by the applicant as a postmarketing commitment (PMC) to assess human factors issues that may affect preparation and administration of the 0.25mL dose in children 2 months to < 3 years of age (see section 5.2).

Seizure and febrile seizure/convulsion are labeled events in the USPI. Other neurological conditions listed in the PVP as potential risks are based on the manufacturer's assessment of pre-licensure clinical trials, postmarketing safety monitoring, published literature, and known product-class effects. One serious adverse event of CNS inflammation (later identified as multiple sclerosis) was reported in clinical trials, assessed as not related. There are few postmarketing reports of encephalitis and GBS, with confounders present, that precluded definitive causal association.

The important potential risks listed in Table 1 are monitored with routine safety surveillance, including review of adverse event reports submitted to FDA, manufacturer submitted periodic safety reports, published literature, and data mining. Please see section 5.2 for discussion of postmarketing commitment (PMC) studies. There are no postmarketing requirements (PMRs) for safety-related studies or Risk Evaluation and Mitigation Strategy (REMS) for Ixiaro.

5.2 Postmarketing Studies

Completed postmarketing studies:

- Applicant has fulfilled the pediatric study requirements, which were put in place at the March 30, 2009 BL 125280/0 approval for use in individuals >17 years of age, for all relevant pediatric age groups for this application.
- Applicant has fulfilled the following postmarketing commitments (PMCs), which were also listed in the BL 125280/0 approval letter dated March 30, 2009:
    - PMC #4: Department of Defense (DoD) Active Safety Surveillance Study in 20,000 study participants

- PMC # 5: DoD Pregnancy Surveillance Study

Final study reports were reviewed under STN 125280/238 (PMCs were fulfilled on July 10, 2018).

No new safety concerns were identified from the above completed postmarketing studies.

Ongoing postmarketing commitment: Applicant conducted the following study as a PMC listed in the BL 125280/125 approval letter dated May 17, 2013 (for use in individuals 2 months to <17years of age):

- PMC#1: postmarketing assessments of human factors issues that may affect preparation and administration of the 0.25mL dose

The final study report for the above human factors study to assess preparation and administration of the 0.25 mL dose of Ixiaro was reviewed and the factors assessment identified concern for potential administration errors, and CBER determined that the sponsor should conduct a second human factors study. There have been delays in initiating the second study due to the COVID-19 pandemic, and FDA is engaged in discussions with the applicant on projected timeline for this study.

Reviewer comment: There were few VAERS reports in individuals < 3 years of age (n = 6), and these reports were individually reviewed. There were 2 serious non-fatal reports (discussed in section 6.2.2 of memo). There were 4 U.S. non-serious reports, of which 1 report was related to incorrect dose administration: a dose of 0.5mL was reported to have been administered to a 1.5-year-old boy when the correct dose is 0.25mL. The child did not experience a clinical adverse event.

6 ADVERSE EVENT REVIEW

6.1 Methods

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event reports following use of Ixiaro between April 13, 2018 to May 31, 2023. VAERS stores postmarketing adverse events and medication errors submitted to FDA and CDC for all approved vaccines. These reports originate from a variety of sources, including healthcare providers, consumers, and manufacturers. Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in VAERS may not be medically confirmed and are not verified by FDA. FDA does not receive reports for every adverse event or medication error that occurs with a vaccine. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Also, there is no certainty that the reported event was actually due to the vaccine.

6.2 Results

The results of the VAERS search of AE reports for Ixiaro during the safety review period are listed in Table 2 below. There were 277 reports, including 186 U.S. and 91 foreign reports, received during the review period April 13, 2018 to May 31, 2023.

Table 2: Ixiaro VAERS reports during April 13, 2018 to May 31, 2023

Age	Serious Non-Fatal*		Deaths		Non-Serious		Total Reported	
	US	Foreign	US	Foreign	US	Foreign	US	Foreign
<17 years	3	5	0	0	17	0	20	5
≥ 17 years	23	50	0	0	133	0	156	50
Unknown	4	35	0	0	6	1	10	36
All Ages	30	90	0	0	156	1	186	91

*Note: Serious non-fatal adverse events include life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, or significant disability or otherwise medically important conditions (OMIC).

6.2.1 Deaths

There were no deaths reported during the safety review period.

6.2.2 Serious Non-fatal Reports

During the safety review period, there were 30 U.S. and 90 foreign serious non-fatal reports. The majority of serious reports (n = 73) involved adults, and 8 reports involved pediatric individuals. Age was unknown in the remaining 39 reports.

The 8 pediatric serious non-fatal cases included:

- 16-year-old female who developed migraines and fibromyalgia
- 16-year-old male experienced syncope post-vaccination with multiple vaccines, including Ixiaro and Gardasil9, and sustained a fall; it was reported that he “fainted from treatment bed...and hit face on the floor knocking out two front right teeth.”
- 15-year-old male experienced syncope post-vaccination
- Fetal disorder with brain malformation in an infant born to a mother who is reported to have received Ixiaro a few weeks prior to conception. (Limited clinical details were provided in this report.)
- 9-year-old male with aseptic meningitis. No additional narrative was provided in this foreign report.
- 15-year-old male developed encephalopathy 11 days following administration of Ixiaro and other concomitant vaccines. Reported to have had a history of viral meningitis. Outcome is reported as recovered from encephalopathy.
- 10-year-old female with abdominal pain, headache, fever, photophobia
- 2-year-old male was diagnosed with Kawasaki's syndrome

Reviewer comments: Review of the cases did not reveal new safety concerns for Ixiaro. Syncope (fainting) may occur in association with administration of injectable vaccines. Syncope has been reported following HPV vaccination and is a labeled event for Gardasil9, which in one case was concomitantly administered with Ixiaro.
Limited clinical details were provided, and in some cases alternate etiologies for the adverse events were present, including pre-existing conditions, such as viral infections, and/or concomitant products administered to the individuals.

The most common Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) for serious reports (all ages) are displayed in Table 3. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 3: Most frequently reported PTs in serious reports

Preferred Term (PT)	# Serious Reports	Label Status *USPI updated September, 2018*
Pyrexia	23	Labeled as *Fever*
Headache	14	Labeled
Dizziness	13	Labeled
Pain in extremity	12	Unlabeled
Influenza like illness	12	Labeled
Chills	11	Labeled
Nausea	10	Labeled

Note: PTs occurring with a frequency ≥10 reports are shown in above table.

Reviewer comments: Most PTs are labeled events or consistent with a labeled event. The unlabeled PT for “Pain in extremity” may be related to labeled events for pain and injection site reactions.

6.2.3 Non-serious Reports

During the safety review period, there were 156 U.S. non-serious reports and a single foreign non-serious report. There were 17 reports in pediatric individuals, 133 reports in adults; age was unknown for the remaining 7 reports.

Table 4 below lists the 10 most frequently reported PTs in non-serious reports. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 4: Most frequently reported PTs in non-serious reports

Preferred Term (PT)	# Non-serious Reports	Label Status *USPI updated September, 2018*
Rash	26	Labeled
Dizziness	23	Labeled
Nausea	20	Labeled
Pyrexia	18	Labeled as *Fever*
Erythema	14	Labeled

Preferred Term (PT)	# Non-serious Reports	Label Status *USPI updated September, 2018*
Pruritus	14	Labeled
Urticaria	13	Labeled as *Itching*
Dyspnea*	12	Unlabeled
Fatigue	12	Labeled
Headache	12	Labeled
Injection site erythema	12	Labeled as *Injection site reactions*
Pain	12	Labeled as *Injection site pain, muscle pain*

Note: Top 10 most frequently reported PTs are shown in above table.
*Exact MedDRA PT is Dyspnoea

Reviewer comments: Most PTs are labeled events or consistent with a labeled event. The unlabeled PT for *dyspnea* is related to labeled events for *difficulty breathing, wheezing*.

6.3 Data mining

Data mining was performed to evaluate whether any reported events following the use of Ixiaro were disproportionally reported compared to other vaccines in the VAERS database. The background database contains VAERS reports since 1990. Disproportionality alerts do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation. A query of Empirica Signals Management with the *US VAERS Vac Name* run with a data lock date of June 23, 2023, for Japanese Encephalitis (IXIARO) identified a single PT with a disproportional reporting alert (EB05>2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean):

- Dermatitis (n = 7 reports).

Reviewer comments: Though the term *Dermatitis* is unlabeled in the USPI, it is related to other labeled events such as *Hives, Rash, Itching*. Most of the seven reports for dermatitis indicated that the patients experienced erythematous rash/hives with pruritis, which were self-limited and resolved. Some reports indicated multiple concomitant vaccine administrations that may have contributed to the skin lesions. There are no new safety concerns from data mining results.

6.4 Periodic safety reports

The manufacturer's postmarketing periodic safety reports for Ixiaro were reviewed. The AEs reported were consistent with those seen in VAERS. No additional safety issues were identified, and no actions were taken by the sponsor for safety reasons.

7 LITERATURE REVIEW

A search of the US National Library of Medicine's PubMed.gov database on July 3, 2023 for peer-reviewed literature, with the search term "Ixiaro" and "safety" limited by human species, and dates from PAC trigger (December 21, 2018) to date of search (July 3, 2023), retrieved 4 publications pertaining to safety. No new safety concerns for Ixiaro were identified in the review of these publications, summarized in the table below:

Publication	Authors' Safety Conclusion
Kling K, Harder T, Younger Z, Burchard G, Schmidt-Chanasit J, Wichmann O. Vaccination against Japanese encephalitis with IC51: systematic review on immunogenicity, duration of protection and safety. J Travel Med. 2020 Mar 13;27(2):taaa016. doi: 10.1093/jtm/taaa016. PMID: 32043122.	The authors conducted a systematic review on the immunogenicity and safety of IXIARO. A total of 32 studies from 16 countries met the inclusion criteria (15 RCTs, 17 non-randomized studies). Rates of serious adverse events were below 5% in all age groups, with the majority not being causally related to the vaccine.
Taucher C, Barnett ED, Cramer JP, Eder-Lingelbach S, Jelinek T, Kadlecek V, Kiermayr S, Mills DJ, Pandis D, Reiner D, Dubischar KL. Neutralizing antibody persistence in pediatric travelers from non-JE-endemic countries following vaccination with IXIARO® Japanese encephalitis vaccine: An uncontrolled, open-label phase 3 follow-up study. Travel Med Infect Dis. 2020 Mar-Apr;34:101616. doi: 10.1016/j.tmaid.2020.101616. Epub 2020 Mar 7. PMID: 32156630.	In this open-label follow-up study, a subset of 23 children who received a 2-dose primary series of IXIARO in the parent study, were evaluated for safety and neutralizing antibody persistence for 36 months. No long-term safety concerns were identified.
Taucher C, Kollaritsch H, Dubischar KL. Persistence of the immune response after vaccination with the Japanese encephalitis vaccine, IXIARO® in healthy adults: A five year follow-up study. Vaccine. 2019 May 1;37(19):2529-2531. doi: 10.1016/j.vaccine.2019.03.030. Epub 2019 Apr 5. PMID: 30962094.	This 5-year follow-up study included individuals who had completed a full primary vaccination series in two preceding studies, IC51-301 or IC51-302, and enrolled a total of 181 subjects. This study did not identify any long-term safety concerns. Authors concluded that data indicated that vaccination with IXIARO is able to induce protective titers that persist up to 60 months after the primary immunization.
Seshadri S, Martin SW, Hills SL, Collins LC Jr. Comparative frequency of specified adverse events following Vero cell culture-derived Japanese encephalitis and Vi capsular polysaccharide typhoid vaccines in U.S. military personnel, July 2011-August 2019. Vaccine. 2023 Feb 24;41(9):1537-1540. doi: 10.1016/j.vaccine.2023.01.061. Epub 2023 Jan 30. PMID: 36725428.	The authors retrospectively compared rates of hypersensitivity and neurologic AEs within 28 days following vaccination of military personnel with Ixiaro or parenteral Vi capsular polysaccharide typhoid vaccine administered without other vaccines. Rates of most events were similar between the vaccines. Only delayed hypersensitivity reactions occurred more frequently following Ixiaro (rate ratio: 4.2, 95 % CI 1.2-15.3; p = 0.03), but rates were low for both vaccines. The authors concluded that these results support Ixiaro's safety.

8 CONCLUSION

This postmarketing pediatric safety review was triggered by the approval of the sBLA 125280/235 on April 13, 2018, for use of Ixiaro booster dose in individuals <17 years of age who are at risk of continued exposure or re-exposure to JEV. Review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for Ixiaro does not indicate any new safety concerns. Adverse events were generally consistent with the safety data in pre-licensure studies and listed in the label. There were no deaths reported during the safety review period.
No unusual frequency, clusters, or other trends for adverse events were identified that would suggest a new safety concern.

9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of Ixiaro.