

Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

Summary Basis of Regulatory Action (SBRA)

Date: October 2, 2018

From: Sudhakar Agnihothram, Ph.D.
Chair of the Review Committee

BLA/ STN#: 125280/251

Applicant Name: Valneva Austria GmbH

Date of Submission: December 4, 2017

Goal Date: October 4, 2018

Proprietary Name: IXIARO

Established Name: Japanese Encephalitis Vaccine, Inactivated, Adsorbed

Indication: IXIARO is a vaccine indicated for active immunization for the prevention of disease caused by Japanese encephalitis virus (JEV) for use in persons 2 months of age and older.

Recommended Action: The Review Committee recommends approval of this supplement.

Offices Signatory Authority: Doran Fink M.D., Ph.D.
Deputy Director-Clinical
Division of Vaccines and Related Products
Applications
Office of Vaccines Research and Review
Center For Biologics Evaluation and Research

- I concur with the summary review.**
- I concur with the summary review and include a separate review to add further analysis.**
- I do not concur with the summary review and include a separate review.**

The table below indicates the material reviewed when developing the SBRA.

Document title	Reviewer name, Document date
Clinical Review	Sixun Yang, M.D., 10/03 /2018
Statistical Review (Assay)	Charles (Yin Kiu) Cheung, Ph.D., 08/27/2018
Statistical Review (Clinical)	Charles (Yin Kiu) Cheung, Ph.D., 08/30/2018
Bioresearch Monitoring Review	Bhanu Kannan, 08/10/2018

Labeling – Advertising, Promotion and Labeling Branch (APLB) review	Michael Brony, 03/07/2018
Assay Review (Rabies)	Alena Dabrazhynetskaya, Ph.D., 02/16/2018
Assay Review (JEV)	Li Yu, M.D., Ph.D., 09/10/2018

1. INTRODUCTION

IXIARO (Japanese Encephalitis Vaccine, Inactivated, Adsorbed) is a formalin-inactivated, aluminum-adsorbed vaccine produced in Vero cells using the attenuated Japanese encephalitis virus strain, SA₁₄₋₁₄₋₂. IXIARO is a vaccine indicated for active immunization for the prevention of disease caused by Japanese encephalitis virus (JEV). IXIARO is approved for use in individuals 2 months of age and older. The primary immunization series consists of two 0.5 mL doses administered intramuscularly 28 days apart for persons 3 years of age and older, and two 0.25 mL doses administered intramuscularly 28 days apart for infants and children 2 months to <3 years of age. Additionally, a booster dose is approved for individuals 14 months and older who have completed the primary immunization series more than 11 months prior and who are at risk for ongoing exposure or re-exposure to JEV. Since travelers who have a short notice of travel to regions where JEV is endemic may not be able to complete the approved Day 28 primary series schedule for IXIARO, an accelerated primary vaccination series remains a need for these individuals.

In this submission, Valneva Austria GmbH seeks to update the Package Insert (PI) to include an alternate primary immunization schedule (two 0.5 mL doses, 7 days apart) for IXIARO in individuals 18 through 65 years of age and to include data supporting the concomitant administration of IXIARO with rabies vaccine administered for pre-exposure prophylaxis. Data to support the proposed alternate schedule are from Study V49_23 sponsored by Novartis and are based on non-inferior seroconversion rate (SCR) to JEV [defined as a Plaque Reduction Neutralization Test (PRNT₅₀) titer of $\geq 1:10$] induced by two 0.5 mL doses of IXIARO administered at 7 days apart concomitantly with Rabipur [inactivated rabies vaccine, marketed in the United States (U.S.) as RabAvert] administered at days 0, 3 and 7 (non-U.S. approved vaccination schedule), compared with IXIARO administered alone according to the approved schedule (two 0.5 mL doses 28 days apart). Valneva also proposes to update the PI with safety data and immunogenicity data from the same clinical study that supports concomitant administration of IXIARO, days 0 and 28 primary immunization schedule, with rabies vaccine.

2. BACKGROUND

JEV, a mosquito-borne flavivirus, causes mostly asymptomatic infection but rarely causes viral encephalitis with fatality rates of 20-30% and serious neurological sequelae in 30-50% of survivors. No licensed antivirals are available, and current clinical intervention is limited to supportive measures for reducing intracerebral pressure and prevention of secondary infections. In Asia, JEV remains the most common cause of viral encephalitis with pediatric incidence of 5-50 cases/100, 000 children per year. Although JEV infections remain absent in North America, children and adults in the U.S. are at risk of infection when traveling to endemic regions. The

Centers for Disease Control and Prevention records indicate 12 cases of travel-related infection in U.S. travelers between 1993-2017. Sixty seven percent of the cases occurred during travel greater than 1 month during the summer season, which is considered the season for transmission of JEV. Two vaccines for prevention of disease caused by JEV, IXIARO and JE-VAX, have been licensed for use in the U.S.

JE-VAX was licensed for use in individuals one year of age and older, based on the protection of the JEV disease in Thai Children with an efficacy estimate of 91%. A PRNT₅₀ titer of $\geq 1:10$ is broadly accepted by regulatory agencies as a surrogate measure of JE vaccine efficacy, and FDA is in agreement with defining seroconversion (SCR) as a PRNT₅₀ titer of $\geq 1:10$. JE-VAX is no longer manufactured, and all remaining stocks expired in February 2011.

Regulatory History

Approval of IXIARO by the U.S. FDA (March 30, 2009) was based on demonstration of non-inferiority to JE-VAX, as measured by SCR and geometric mean neutralizing antibody titer (GMT) at 28 days post completion of the primary series. The initial indication was for use in individuals 17 years of age and older. The inclusion of the long-term immunogenicity data in the PI and the use of a booster dose in persons 17 years of age and older was approved under the efficacy supplement STN 125280/19 on October 14, 2010. The extension of the approved indication for primary series vaccination to include infants, children, and adolescents two months to less than 17 years of age was approved under the efficacy supplement STN 125280/125 on May 17, 2013. A booster dose for children and adolescents 14 months to less than 17 years of age and inclusion of longer-term pediatric immunogenicity data in the PI were approved under efficacy supplement STN 125280/235 on April 13, 2018.

Pre-submission Regulatory Activities:

- January 26, 2010 - Joint FDA/EMA Scientific Advice Meeting - Consensus obtained on the proposed primary endpoint, SCR as determined by JEV-neutralizing antibodies at 28 days after the last IXIARO vaccination, and the non-inferiority study design (conventional schedule as a comparator). The alternate (days 0 and 7) primary series schedule was subsequently authorized by the European Medicines Agency for use in adults 18 through 65 years of age.
- August 04, 2015 - Type C meeting was held to discuss the pediatric requirements, the alternate immunization schedule, and the acceptability of the non-IND study V49-23 to support the labeling update. CBER communicated that the non-IND study would support a labeling update if the study was conducted under Good Clinical Practice (GCP) and the data format complies with the FDA requirements.
- April 12, 2016 - Valneva submitted an initial pediatric study plan (iPSP) for review, where they stated that PREA requirements did not apply to the alternate vaccination regimen because IXIARO has been granted an orphan-drug status. The agreed iPSP was accepted by FDA on May 9, 2016.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

No new manufacturing changes were submitted to this supplement.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

No new nonclinical pharmacology/toxicology studies were performed in support of this supplement.

5. CLINICAL PHARMACOLOGY

No new clinical pharmacology information was provided in this supplement.

6. CLINICAL/ STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

One non-IND clinical study, V49_23, which was sponsored by Novartis, was submitted to support labeling changes in this efficacy supplement.

V49_23 was a phase 3, multicenter, observer-blind clinical trial performed to assess the safety and immunogenicity of IXIARO and Rabipur [Inactivated Rabies Vaccine, manufactured by Novartis (acquired by GSK in March 2018), marketed in the U.S. as RabAvert] administered concomitantly or separately according to either approved (conventional) or alternate (accelerated) schedules to healthy adult subjects 18 through 65 years of age. A total of 661 subjects were randomized at a 3:4:4:1 ratio into one of the following groups as described in Table 1. RabAvert has a licensed primary vaccination regimen of three doses (1.0 mL each), administered at Day 0, 7, and 21 or 28, so in the R/JE-Acc treatment group, Rabipur was administered on a non-U.S.-licensed schedule.

Table 1: Clinical Study Design

Groups	Planned	Enrolled	Schedule	Vaccines	Day 4 (Visit 2)	Day 8 (Visit 3)	Day 29 (Visit 4)
R/JE-Conv	N=165	N=167	Conventional (Rabies + JE Vaccines)	Rabies JE	Placebo	Rabies Placebo	Rabies JE
R/JE-Acc	N=220	N=217	Accelerated (Rabies + JE Vaccines)	Rabies JE	Rabies	Rabies JE	Placebo Placebo
R-Conv	N=220	N=221	Conventional (Rabies Vaccine alone)	Rabies Placebo	Placebo	Rabies Placebo	Rabies Placebo
JE-Conv	N=55	N=56	Conventional (JE Vaccine alone)	JE Placebo	Placebo	Placebo Placebo	JE Placebo

Source: Table 2-1, pp 19 of the clinical study report V49_23 submitted to BLA 125280/251.0

Analyses of Primary and Secondary Endpoints

Neutralization assays for assessing clinical endpoints

The Standard Operating Procedure (SOP) for the anti-JEV PRNT (VIE-CIL-SOP-0006) that was submitted to the original BLA was used in V49_43. VIE-CIL-SOP-0006 and the re-validation report of the PRNT, VALM_IC51-001_002_VRe-01, were reviewed by the product reviewer under the STN 125280/235 in August of 2017. The assay reviewer in this file did not identify any issues with the SOP. For Rabipur, the immunogenicity endpoints were assessed in a validated assay previously reviewed and found acceptable by CBER under the IND 15026, amendment 38. The assay validation information submitted under this efficacy supplement was reviewed by the same product reviewer who had reviewed the information submitted to the IND 15026, amendment 38. No concerns were raised by the statistical assay reviewer.

Anti-JEV neutralizing antibodies

The primary endpoint was SCR to JEV, which is defined as the proportion of subjects with an anti-JEV neutralizing PRNT₅₀ titer $\geq 1:10$. The pre-specified non-inferiority criterion for the primary endpoint was a lower bound (LB) greater than -10% for the two-sided 97.5% CI of the difference in SCR between R/JE-Acc and JE-Conv groups. The major secondary endpoint was non-inferiority comparison of PRNT₅₀ GMT between R/JE-Conv and JE-Conv groups. The pre-specified non-inferiority criterion for the major secondary endpoint was a LB greater than 0.5 for the two-sided 95% CI of the PRNT₅₀ ratio [(R/JE-Conv)/(JE-Conv)]. Both the primary and the secondary endpoints were measured at 28 days after the last IXIARO injection.

At 28 days after the last IXIARO administration, 99% (97.5% CI: 96%, 100%) of subjects immunized concomitantly with rabies vaccine according to the accelerated schedule (R/JE-Acc) were seroconverted with a PRNT₅₀ GMT of 690 (95%CI: 595, 801), while 100% (97.5% CI: 93%, 100%) of subjects immunized with the conventional schedule alone (JE-Conv) were seroconverted with a PRNT₅₀ GMT of 331 (95%CI: 2265, 415). At 28 days after last IXIARO administration, 100% (97.5% CI: 98%, 100%) of subjects immunized concomitantly with rabies vaccine according to conventional schedule (R/JE-Conv) were seroconverted with a PRNT₅₀ GMT of 291 (95% CI: 256, 331). Both the primary and secondary endpoints met the pre-specified non-inferiority criteria. Furthermore, the durability of the antibody response generated from the accelerated schedule of IXIARO by the presence of PRNT₅₀ titer of $\geq 1:10$ at one year after the primary immunization series was reported in 94% (97.5% CI of 90% to 97%) of the study participants.

Since the accelerated schedule of IXIARO (two doses 7 days apart) was not assessed as a stand-alone comparator, safety and effectiveness of the IXIARO accelerated schedule was inferred from the accelerated concomitant vaccination (R/JE- Acc group) data. At 7 and 28 days after last IXIARO administration, PRNT₅₀ GMT titers in the R/JE-Acc group were 715 (95% CI: 608, 842) and 690 (95% CI: 595, 801), respectively, compared to 292 (95% CI: 247, 346) and 299 (95% CI: 254, 352), respectively, in the R/JE-Conv group and 376 (95% CI: 277, 510) and 337 (95% CI 252, 451), respectively, in the JE-Conv group. While the anti-JEV antibody responses

in the R/JE-Acc group were found to be unexpectedly higher compared to the R/JE-Conv group, raising the question of whether concomitant vaccination with rabies vaccine enhanced the antibody response to IXIARO, the anti-JEV antibody responses in the R/JE-Conv group were similar to those in the JE-Conv group. Furthermore, peak anti-rabies antibody GMCs were similar across all of the groups vaccinated with Rabipur (R/JE-Acc 26; R/JE-Conv 21 ; R-Conv 24) indicating concomitant rabies vaccination with IXIARO according to the accelerated or conventional schedules did not enhance the immune response to rabies vaccine. Given these observations, the immunogenicity data from the R/JE- Acc group was accepted in support the use of accelerated schedule of IXIARO.

Anti-rabies antibodies

A rabies virus neutralizing antibody (RVRNA) titer of ≥ 0.5 IU/mL is generally considered as a reasonable evidence of protection against rabies disease, and seroconversion to rabies is defined as a GMC ≥ 0.5 IU/mL as determined by a (b) (4) assay. The primary endpoint for rabies vaccination was the non-inferiority comparison between R/JE-Acc and R-Conv groups of the percentage of subjects with RVRNA titer of ≥ 0.5 IU/mL. The major secondary endpoint was non-inferiority comparison of RVRNA GMCs between R/JE-Conv and R-Conv groups. The primary endpoint was measured at 7 days after the last rabies vaccination, and the secondary endpoint was measured at 28 days after the last rabies vaccination. Seroconversion rates among subjects in the R/JE-Acc group were 100% (97.5% CI:97%, 100%) with a mean GMC of 26 (97.5% CI: 22, 30) and in the R-Conv group were 100%, (97.5% CI: 97%, 100%), with a mean GMC of 13 (97.5% CI:11, 15). The lower limit of the two-sided 97.5% CI on the group differences in seroconversion rate was -2.8%, which was above the pre-specified non-inferiority margin set at -5%. Since the schedule for rabies vaccine used in the R/JE-Acc group is not U. S. licensed, this non-inferiority analysis cannot support concomitant administration of the IXIARO accelerated primary series schedule with rabies vaccine, and will not be included in the PI. RVRNA GMCs measured at 28 days after the last Rabipur vaccination comparing Rabipur alone vs. Rabipur concomitantly administered with IXIARO according to the conventional schedule was 9.9 and 11, respectively. The lower bound of the 2-sided 95% CI of the GMC ratio for [(R/JE-Conv)/(R-Conv)] was 0.86, which was greater than the pre-specified non-inferiority margin set at 0.667. Since the schedule for rabies vaccine used in the R/JE-Conv group is a U.S.-licensed schedule, this non-inferiority analysis supports concomitant administration of IXIARO, days 0 and 28 primary series, with rabies vaccine.

b) Pediatrics

Since use of IXIARO was granted an orphan-drug designation in the pediatric population, PREA pediatric study requirements do not apply to this new alternate primary series dosing regimen.

c) Other Special Populations

N/A

d) Bioresearch Monitoring Review (BIMO)

A Bioresearch Monitoring (BIMO) inspection was conducted at one foreign clinical study site that participated in the conduct of study Protocol V49-23. The inspection did not reveal any issues that impact the data submitted in this supplemental Biologics License Application (sBLA).

7. SAFETY

All but one subject in the R/JE-conv group were exposed to one of the study vaccines, and all exposed subjects were included in the analysis of solicited and unsolicited safety sets except for one subject in the R-conv group for whom safety data was not available. Percentages of subjects experiencing at least one solicited Adverse Events were 85% in the R/JE-Acc group, 83% in the R/JE-Conv Group, 82% in the R-Conv group and 79% in the JE-Conv group. Similarly, the percentages of subjects reporting unsolicited AEs from Day 1 through Day 57 were 42% in the R/JE-Conv Group, 50% in both R/JE-Acc and R-Conv groups, and 52% in the JE-Conv group. Among the subjects who reported unsolicited AEs, 11% (JE-Conv), 23% (R/JE-Acc), 18% (R/JE-Conv), and 22% (R-Conv) of subjects reported at least possibly or probably related unsolicited AEs as assessed by the investigator. This observation indicated that the increased rates in the concomitant vaccination groups were likely attributable to rabies vaccine. The most frequently reported unsolicited AEs were in system organ class (SOC) "Infections and Infestations" followed by general disorders and Administrative Site Conditions. The most frequently reported unsolicited Adverse Events (AE) by preferred term were nasopharyngitis (13 to 15% across all groups) and headache (7 to 10%). Among ten SAEs reported overall, 3 SAEs, 1 in the JE-Conv group (eyelid edema, pruritus generalized) and 2 in the R-Conv group (subject 1: atrial fibrillation, subject 2: syncope, tachycardia), were assessed by the clinical reviewer as at least possibly related to vaccination. All at least possibly or probably related SAEs were resolved by end of the study. Concomitant vaccination with IXIARO and Rabipur was associated with numerically higher rates of adverse reactions than IXIARO alone, but similar to rates of adverse reactions to Rabipur administered alone.

8. ADVISORY COMMITTEE MEETING

This supplement did not require input from the Vaccines and Related Biological Products Advisory Committee.

9. OTHER RELEVANT REGULATORY ISSUES

None.

10. LABELING

The PI submitted to the supplement included the following major changes:

- a. Highlights - Inclusion of details regarding the alternate primary series dosing regimen in the table under "Dosage and Administration."
- b. Section 2 - Dosing instructions added regarding the use of the alternate primary series dosing regimen.

- c. Section 6 - Safety data from the study V49_23 investigating a rapid immunization schedule of IXIARO and concomitant administration with rabies vaccine in adults 18-65 years of age.
- d. Section 7.2- Statement indicating that co-vaccination of IXIARO and inactivated vaccine Rabipur is safe, and no immune interference of the two vaccines has been observed.
- e. Section 14- Immunogenicity data from the study V49_23.

Revised changes to the PI were agreed upon after labeling negotiations with the applicant. The PI that was submitted in amendment 13 on October 1, 2018, was found to be acceptable. The APLB reviewer found the prescribing information to be acceptable from a promotional and comprehension perspective. There was no change to the carton and container label.

11. RECOMMENDATIONS AND RISK/BENEFIT ASSESSMENT

a) Recommended Regulatory Action

The Review Committee recommends the approval since no concerns were raised during the review of this supplement, and the benefits from the alternate schedule outweigh the risks.

b) Risk Benefit Assessment

The clinical benefit of the alternative IXIARO primary series schedule is demonstrated by the presence of a PRNT₅₀ titer of $\geq 1:10$ at 28 days after the primary immunization series in 99% (97.5% CI of 96% to 100%) of the study participants. Regardless of age, race and ethnicity, the antibody response following the completion of the vaccination of IXIARO from the alternate schedule was non-inferior when compared with the antibody response from the approved schedule.

The safety and effectiveness of IXIARO alternate primary series schedule was inferred from the concomitant vaccination data since IXIARO accelerated schedule (two doses of IXIARO administered seven days apart) alone was not assessed as a comparator. Adverse reactions observed in the R/JE-Acc group were mild to moderate and included injection site pain and erythema, fatigue, headache and myalgia, which resolved within several days. Eyelid edema and pruritus were reported in one subject and were concluded to be related to IXIARO, which is known to cause hypersensitivity reactions rarely. No neurological adverse events were reported in the IXIARO group.

The data submitted to this efficacy supplement support the concomitant administration of IXIARO, days 0 and 28 primary series schedule, with the U.S.-licensed schedule for RabAvert. The accelerated schedule of rabies vaccine used in the clinical study is not licensed for use in the U.S. population. Hence, the data are not adequate to support concomitant administration of IXIARO, days 0 and 7 primary series schedule, with rabies vaccine.

IXIARO is the only licensed vaccine available in U.S. for the prevention of disease caused by JEV, which has a 30% fatality rate and risk of permanent neurologic

sequelae in non-fatal cases. Since the licensed primary series vaccination schedule (two doses 28 days apart) may not be feasible for travelers with a short notice for travel to JEV endemic regions, licensure of the alternate schedule (two doses 7 days apart) will address this unmet medical need in individuals 18 through 65 years of age. The substantial benefit of the prevention of JEV disease in travelers to JEV endemic areas outweighs the risks due to the generally mild adverse reactions and rare hypersensitivity reactions.

c) Recommendation for Postmarketing Activities

Based on the information contained in this application, no changes to the pharmacovigilance plan originally submitted for IXIARO are recommended.