Approval Date: October 4, 2018

Product: IXIARO

Proper Name: Japanese Encephalitis Vaccine, Inactivated, Adsorbed

Manufacturer: Valneva Austria GmbH

Indication: For the prevention of disease caused by Japanese encephalitis virus in persons 2 months of age and older.

Description: IXIARO, Japanese Encephalitis Vaccine, Inactivated, Adsorbed is a sterile suspension for intramuscular injection. IXIARO is a vaccine prepared by propagating JEV strain SA14-14-2 in Vero cells. Multiple viral harvests are pooled, clarified and concentrated.

BLA: BL 125280

Regulatory Milestone:

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 gemometric 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 JEVneutralizing 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 orphandrug status. The agreed iPSP was accepted by FDA on May 9, 2016.

PDUFA Goal Date: October 4, 2018

Package Insert: Package Insert and Patient Information - IXIARO

Summary Basis for Regulatory Approval: October 2, 2018 Summary Basis of Regulatory Action - IXIARO

European Public Assessment Report: Human medicine European public assessment report (EPAR): Ixiaro

Advisory Committee:

CBER did not present these data to an Advisory Committee because the review of information submitted in this submission did not raise concerns or controversial issues which would have benefited from an advisory committee discussion.

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/JEConv), 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.

NCT Numbers:

- NCT03971058
- NCT01559831
- NCT01335412
- NCT01158599
- NCT01386827
- NCT01398540
- NCT01296360
- NCT00319592
- NCT01396512
- NCT00314145
- NCT03204227
- NCT01656200
- NCT00604708
- NCT04223037
- NCT03282370
- NCT02526550
- NCT02880865
- NCT01246479
- NCT01041573
- NCT02816554
- NCT02532569
- NCT01943305
- NCT01943825
- NCT02367664
- NCT01047839
- NCT01214850
- NCT00694460
- NCT00621764
- NCT00595270
- NCT00596102
- NCT00605085
- NCT00249769
- NCT02963909
- NCT03296410
- NCT00735644
- NCT01662440
- NCT01408537
- NCT01092507
- NCT02039440
- NCT00594958
- NCT00595309
- NCT00595465
- NCT00776230
- NCT00595790
- NCT00596271
- NCT00740155
- NCT00703521
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- NCT02643433
- NCT00981630
- NCT00982137
- NCT00412516
- NCT02545517
- NCT01150942
- NCT00463476
- NCT00314132
- NCT01466387
- NCT00384670
- NCT00463684
- NCT01567865
- NCT00981175
- NCT04111432
- NCT03519568

EudraCT Numbers:

- 2013-001954-88
- 2010-023300-27
- 2016-002894-36
- 2010-020450-33
- 2017-002137-32
- 2010-022265-10
- 2010-018630-52
- 2011-000475-14
- 2013-004366-34

- 2009-015588-15
- 2009-015595-10
- 2011-005173-23
- 2010-022266-27

Publications:

- Erra, E. O., Askling, H. H., Rombo, L., Riutta, J., Vene, S., Yoksan, S., Lindquist, L., Pakkanen, S. H., Huhtamo, E., Vapalahti, O., & Kantele, A. (2012). A single dose of vero cell-derived Japanese encephalitis (JE) vaccine (Ixiaro) effectively boosts immunity in travelers primed with mouse brain-derived JE vaccines. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, *55*(6), 825–834. https://doi.org/10.1093/cid/cis542
- Jelinek, T., Cromer, M. A., Cramer, J. P., Mills, D. J., Lessans, K., Gherardin, A. W., Barnett, E. D., Hagmann, S., Askling, H. H., Kiermayr, S., Kadlecek, V., Eder-Lingelbach, S., Taucher, C., & Dubischar, K. L. (2018). Safety and immunogenicity of an inactivated Vero cell_derived Japanese encephalitis vaccine (IXIARO®, JESPECT®) in a pediatric population in JE non-endemic countries: An uncontrolled, open-label phase 3 study. *Travel medicine and infectious disease*, *22*, 18–24. https://doi.org/10.1016/j.tmaid.2018.03.003