

## Toxicology Review of IXIARO Vaccine

BLA125280/235.0/235.4

Type and date of submission: Efficacy supplements; June 16 and September 4, 2017

Sponsor: Intercell, USA, Inc. Gaithersburg, Maryland

Product: IXIARO (Japanese encephalitis vaccine, inactivated, adsorbed)

Cross references: None

Proposed indication for use: Active immunization for the prevention of disease caused by Japanese encephalitis virus

Reviewer: Ching-Long Joseph Sun, Ph. D., Division of Vaccines and Related Products Applications

### Précis

The applicant submitted a proposed package insert in complying with new content and format requirements of the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling for human prescription drug and biological products. The developmental toxicity study report submitted in the original BLA has been reviewed (see review of July 24, 2008 by Dr. Gruber). The toxicology review of this supplement addresses the compliance of new requirements on section 8.1 and suggests revision on section 13.1.

### Review

In according to the guidance for industry of 2014 to assist applicants in complying with new requirements, revision on section 8.1 from a toxicological standpoint is recommended as follow:

#### Pregnancy

##### 2. Risk Summary

###### b. Risk statement based on animal data

“A developmental toxicity study was performed in female rats administered IXIARO prior to mating and during gestation. The dose was 0.5 mL on each occasion (a single human dose is 0.25 mL or 0.5 mL). This study revealed no evidence of harm to the fetus due to IXIARO (see Data).”

##### 4. Data

###### b. Animal data

“In a developmental toxicity study, female rats were administered IXIARO by intramuscular injection 3 weeks and one week prior to mating and on gestation day 6. The dose was 0.5 mL on each occasion (a single human IXIARO dose is 0.25 mL or 0.5 mL). No adverse effects on pre-weaning development up to post-natal day 18 were observed. There were no vaccine-related fetal malformations or variations.”

Accordingly revision on section 13.1 is recommended as follow:

#### 13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

“IXIARO has not been evaluated for its carcinogenic or mutagenic potential. Vaccination of female rats with IXIARO had no effect on fertility [see Use in Specific Populations (8.1)]. The effect of IXIARO on male fertility has not been evaluated.”

Concurrence: Martin David Green, Ph. D., Supervisory Toxicologist, Division of Vaccines and Related Products Applications