PUBLIC ASSESSMENT SUMMARY REPORT Update– Japanese Encephalitis Vaccine (Human) (Purified Inactivated Vaccine-Adsorbed) JEEV®

What is JEEV®?

JEEV® is a vaccine with the following composition:

Components	Quantity /dose(0.5 mL)
Purified Inactivated Japanese Encephalitis Virus Strain (SA14-14-2)	6 µg
Aluminium as Aluminium Hydroxide	0.1% w/v
Phosphate Buffer Saline	q.s

There is also a new formulation of JEEV (3 µg/dose) intended for paediatric administration.

Why has the VPSAR for JEEV® been updated?

At the time of initial prequalification, (12 July 2013), only the adult indication was approved. Subsequently, (March 2015), following review by the Programmatic Suitability for Prequalification Standing Committee (PSPQ-SC), the 6 µg /dose (0.5mL) presentation was approved for prequalification as a two dose paediatric presentation. This followed the prequalification of auto-disable syringes for immunisation able to deliver a 0.25mL dose. The PSPQ-SC recommended that if this formulation was used in supply through the UN for paediatric use, then the requirements described in the subsequent section <<**Handling of the 6 µg / 0.5 mL formulation vaccine as a two-dose preservative-free paediatric presentation**>> should be applied**.** In July 2016, the new formulation containing a single dose of 3 µg / dose (0.5mL) was approved. This formulation could be used in paediatric programmes without the need for the special precautions indicated for use of the 6 µg / 0.5mL presentation.

Container

JE vaccine is dispensed into 3 mL USP Type I clear tubular glass vials which are sealed with 13 mm grey bromobutyl rubber stoppers and capped with aluminium flip-off seals : scarlet red colour (for the 6 µg / 0.5mL formulation); or Blue (for the 3 µg / 0.5mL paediatric formulation).

Real time and accelerated stability reviewed supports the use of a VVM type 14. The VVM is attached to the flip off cap.

Inactivated Bulk manufacture and Formulation occurs in the facility at Azamabad, India

-Filling of the final product occur in the Production Plant at Shameerpet, India

What is JEEV® used for?

JEEV® is indicated for active immunization against Japanese Encephalitis Virus. The age range approved for WHO prequalification is ≥1 to ≤ 49 years.

How is JEEV® used?

≥3 years:
The primary immunization course of JEEV® is administration of two doses of 6μg / 0.5ml each, with the second dose administered 28 days after the first dose. The vaccine is administered intramuscularly. The preferred location is the deltoid muscle of upper arm.

Paediatric:
The primary immunization course of JEEV® is administration of two doses of 3μg / dose each, with the second dose administered 28 days after the first dose. The vaccine is administered intramuscularly. The preferred site for children is the anterolateral aspect of the thigh.

For further information regarding handling of the 6 μg / 0.5mL formulation of the vaccine when delivered as a paediatric dose, please see **Handling of the 6 μg / 0.5 mL formulation vaccine as a two-dose preservative-free paediatric presentation.**

There is no data regarding co-administration of JEEV® with other vaccines.

What are the vaccine characteristics?

JEEV® must be stored between 2-8°C. It must not be frozen. Under these recommended storage conditions, the approved shelf life for the 6μg / 0.5mL formulation is 36 months from the date of manufacture.

To date, the approved shelf life of the 3 μg / dose 0.5mL formulation is 24 months. An extension to be equivalent to the 6 μg / 0.5mL formulation is expected once further stability data from on-going studies are submitted for review.

The vaccine does not contain any preservative.

Cold chain volume per dose in the secondary carton of the 6 μg / 0.5mL formulation is 14.7 cm^3 (adult dose) and 7.35 cm^3 (paediatric dose).

For the 3 μg / 0.5mL formulation, cold chain volume per dose in the secondary carton is 14.7 cm^3

Who is the regulatory authority responsible for its oversight vis a vis WHO?

JEEV® was cleared for license in India, its country of manufacture, by CDSCO on 29 September 2011.

How has JEEV® been studied from the clinical point of view?

JEEV® is the result of a technology transfer of inactivated VERO-cell derived purified, adjuvanted IC51 (IXIARO) vaccine, from Intercell. The IC51 (IXIARO) vaccine has been licensed in several countries based on the similar safety and immune profile compared to the inactivated mouse-brain derived vaccine JEVAX, which is known to be effective against JE.
JEEV® has been shown to be safe in a phase I trial, BECT013, with two doses (6 µg/0.5ml) in healthy adults. A phase II/III study, BECT018, was conducted in young children in India; in that study JEEV® was used at 0.3µg/ 0.25ml in a 2-dose schedule. The limited evidence for immunogenicity and safety currently available for JEEV® was considered sufficient given the acceptance of the degree of similarity between JEEV® and IC51 (IXIARO) in terms of same raw materials (cell banks and virus seed banks), same process flow and compliance of the two vaccines with the same in-process controls and release specifications. A booster dose of IC51 (IXIARO) at month 12 after primary immunization is recommended for adults at continuous risk for acquiring Japanese Encephalitis such as persons residing in endemic areas. By analogy such recommendation may be extended for JEEV®. A phase 3 study IC51 (IXIARO) in children indicated a pronounced booster response when a dose was delivered 12 months following the primary series. The national regulatory authority of reference has not approved an indication for a booster dose for adults or children.

Clinical studies were carried out in support of an indication for 3-17 year olds (6 µg / 0.5 mL dose formulation). These studies showed adequate immune response in terms of sero-conversion, and good safety profile in this age group. A change in indication to include this age group was approved by the Indian authorities and subsequently approved for prequalification purposes.

Other information about evaluation of JEEV®:

As part of the prequalification process for JEEV®, the Product Summary File and the responses provided by manufacturer to observations made by WHO has been reviewed for quality, safety and efficacy by a team of WHO experts, and found to meet WHO requirements of WHO TRS 963, Annex 1.
The manufacturer's manufacturing facility was audited by a WHO team of experts and found to be in compliance with WHO GMP requirements [WHO TRS 822, Annex 3; TRS 961, Annexes 2, 3 and 6].

WHO has conducted independent testing of batches of the vaccine for critical release parameters in contracted laboratories qualified by WHO for the purpose, and results obtained were in compliance with the quality specifications of the product.

Handling of the 6 µg / 0.5 mL formulation of the vaccine as a two-dose preservative-free paediatric presentation.

Prior to the availability of the 3µg / 0.5mL formulation of the vaccine, the PSPQ-SC considered the use of the 6 µg / 0.5 mL formulation of the vaccine in a paediatric population, since that is the preferred target population in endemic countries. They therefore recommended that this presentation was programmatically suitable, provided that similar measures were used as for other two-dose preservative-free vaccine presentations that have been WHO prequalified :

Special attention to training of health care staff is needed for the proper use of two-dose unpreserved liquid presentations. Specific pre-introduction measures are required to assure programmatic readiness is achieved prior to introduction. Post-introduction evaluations and corrective training actions, where needed, are required to assure appropriate continued use of this presentation.

Each country considering introduction of this vaccine presentation will need to ensure its programmatic readiness to do so. Each country will also need to ensure the monitoring of its correct use and implementation of any corrective training needed. To mitigate against potential programmatic risk countries should ensure that they:

- Understand the benefits and potential contamination risks of the two-dose unpreserved presentation and understand the need for special training to enhance immunization worker practices.
- Conduct post introduction evaluations to determine levels of Health Care Worker knowledge and compliance with the correct handling of the vaccine; and implement corrective training if needed.

Prior to introduction countries should:

- Ensure training materials are in place in immunization centres prior to the launch of the vaccine.
- Place stickers on refrigerators at all levels indicating that opened vials of the vaccine must be discarded six hours after opening. The stickers should be in place prior to the launch of the vaccine.

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