6.3 Shelf life

<2 years>

6.4 Special precautions for storage

Store in a refrigerator at 2° - 8° C (35° - 46° F).

Do not freeze. Discard if the vaccine has been frozen.

Do not use the vaccine after the expiration date shown on the label.

Store in the original package in order to protect from light. During storage, a clear liquid with a white sediment can be observed.

7. Presentation

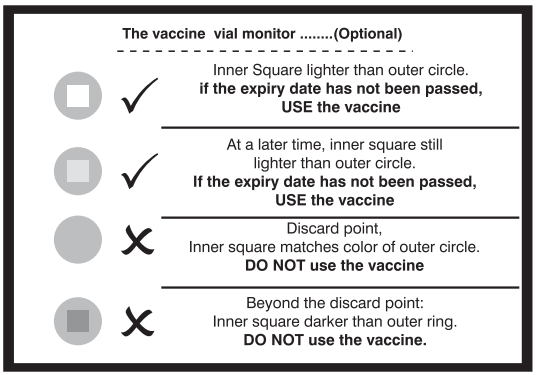
Five dose vial - 2.5 mL

2.5 mL suspension in 3 mL capacity glass vial (USP type 1 glass) with stoppers (Grey Bromobutyl rubber) and flip off Aluminium seal.

Handling of multi dose vial: Once opened, multi dose vials of JEEV® Vaccine from which one or more doses of vaccine have been removed during an immunization session may be used in subsequent immunization sessions for up to a maximum of 4 weeks, provided that all of the following conditions are met:

- the expiry date has not passed
- the vaccines are stored under appropriate cold chain conditions
- the vaccine vial septum has not been submerged in water
- Aseptic technique has been used to withdraw all doses
- The vaccine vial monitor (VVM) has not reached the discard point.

Presentation available with or without vaccine vial monitor.



Vaccine Vial Monitor (VVM) is part of the label. The colour dot appears on the label of the vial, is a VVM. This is a time - temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the ring, then the vaccine can be used. As soon as the colour of the central square is the same colour as the ring or of a darker colour than the ring, then the vial shouldbe discarded.

8. References

1. WHO model Pack Insert

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Manufactured by:
Biological E. Limited
Corporate Address: 18/1 & 3, Azamabad
Hyderabad, Telangana - 500 020, India.
Web: www.biologicale.com

JAPANESE ENCEPHALITIS INACTIVATED VACCINE (Human)
(PURIFIED INACTIVATED VACCINE - ADSORBED)

JEEV®

1. NAME OF THE MEDICINAL PRODUCT

JEEV® is a suspension for injection

Japanese Encephalitis Inactivated Vaccine (Human)

(Purified Inactivated Vaccine - Adsorbed)

2. COMPOSITION

Each 0.5mL contains :

Purified Inactivated Japanese Encephalitis Virus Vaccine Strain (SA_{14}-14-2)[1] :	6 µg
Aluminium as Aluminium Hydroxide	0.1%w/v
Thiomersal BP	0.005% w/v
Phosphate Buffer Saline	q.s.

[1] produced in Vero cells

The vaccine is formalin inactivated

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Suspension for injection

The appearance of the liquid is a white, clear non-uniform suspension which becomes homogenous upon shaking.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

JEEV® (6 µg/0.5 mL) is indicated for active immunization against Japanese encephalitis in children and adults aged between ≥ 3 and ≤ 49 years.

It should be used in children, adolescents and adults at risk of exposure through travel into areas where JE is endemic, spending a month or longer in endemic areas during the transmission season, especially if travel will include rural areas, or in the course of their occupation or residing in areas where JE is endemic or epidemic.

4.2 Posology and method of administration

Method of administration

The vaccine should be administered by intramuscular route. For children ≥ 3 year both anterolateral aspect of thigh and deltoid muscle are preferred sites for injection (if the deltoid muscle mass is adequate). Do not administer intravenously, intradermally or subcutaneously.

Posology

The immunization schedules for JEEV® should be based on official recommendations.

Children, Adolescents & Adults (≥ 3 to ≤ 49 years)

The primary vaccination series consists two separate doses of 0.5mL each according to the following schedule:

First dose: day 0

Second dose: 28 days after first dose

It is recommended that vaccinee who received first dose of JEEV® should receive their 2nd dose of vaccination course with JEEV® only

The vaccine has to be administered by a qualified healthcare professional.

Immunization series should be completed at least week prior to potential exposure to JEV. Before administration, shake the vial well to obtain a white, homogeneous suspension. Do Not administer if particulate matter remains following shaking or if discoloration is observed.

Booster dose recommendation (For Adults of ≥ 18 to ≤ 49 years age):

A booster dose (third dose) should be given between 12 - 14 months after the recommended primary immunization, prior to potential re-exposure to JEV. Persons at continuous risk for acquiring Japanese Encephalitis (Laboratory personnel or persons residing in endemic areas) should receive a booster dose at month 12 after primary immunization.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients or to any residuals (e.g. protamine sulphate).

Individuals who show hypersensitivity reactions after receiving first dose of the vaccine should not be given the second dose.

Vaccine must not be given to indivduals with known or suspected hypersensitivity to any constituent of the vaccine.

Administration must be postponed in persons with acute severe febrile conditions.

4.4 Special warnings and precautions for use

As with all injectable vaccines, appropriate medical treatment and supervision should always be available to treat rare cases of anaphylactic reactions following the administration of the vaccine.

JEEV® is an intramuscular vaccine and under no circumstance be administered intravenously.

As with any other vaccine, vaccination with JEEV® may not result in protection in all cases.

JEEV® will not protect against encephalitis caused by other micro-organisms.

Like other intramuscular injections, this vaccine should not be administered to persons with thrombocytopenia, haemophilia or other bleeding disorders.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies with other medicinal products have not been performed on JEEV®. When JEEV® is administered concomitantly with injectable vaccines, they should be given with separate syringes at different injection sites. JEEV® should not be mixed with any other vaccine in the same vial.

4.6 Pregnancy and lactation

Pregnancy

Safety and effectiveness have not been established in pregnant women and in nursing mothers. In animal studies findings of unclear relevance have been identified for a similar product. As a precautionary measure, the use of JEEV® during pregnancy or lactation should be avoided.

Lactation

It is not known whether this vaccine is excreted in human milk.

4.7 Effects on ability to drive and use machines

No studies on the effects of JEEV® on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The safety of the JEEV® vaccine was assessed in a controlled clinical trial in ≥ 1 to < 3 year old healthy Indian children in comparison with a licensed JE vaccine.

Approximately 21% of vaccinated subjects can be expected to experience adverse reactions based on the clinical data. They usually occur within the first three days after vaccination, are usually mild or occasionally moderate in intensity and disappear within a few days. No increase in the number of adverse reactions was noted between first and second doses.

Most commonly reported local adverse reactions were injection site pain (8.5%) and tenderness (4.6%) and the most commonly reported systemic adverse reaction was pyrexia (11.1%). The other vaccine related adverse events reported were injection site swelling (3.29%), injection site erythema (2.63%), decreased appetite (1.32%), somnolence (1.64%) and rash (1.32%).

In a multi-centre, open label, phase IV study conducted on Indian children (n=108) aged ≥3 years to <18 years, 50% of the subjects experienced at least 1 adverse event, majority being mild in nature.

The most common treatment emergent local adverse events were injection site pain (44.4%), redness (7.41%) and swelling (7.41%). The most common systemic adverse events were myalgia (12.04%), fever (4.63%) and headache (4.63%). There were no serious adverse events reported for any subjects during the entire study period.

In a multicentre, randomized, open label, phase IV study in Indian adults (n=162) aged ≥18 years to <49 years, comparing JEEV® with IXIARO® , both the vaccines were found to have similar adverse event profile. Injection site pain (44.7% in JEEV® vs. 54.2% in IXIARO®) was the most common local adverse event reported and fever (23.7% in JEEV® vs. 29.2% in IXIARO®) was the most common systemic adverse event reported. There were no serious adverse events in either of the study groups during the study period.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Encephalitis Vaccines, ATC Code: J07BA02

Japanese encephalitis is a disease caused by the mosquito-borne Japanese encephalitis virus (JEV). JEEV® is a vero-cell based purified inactivated vaccine that is known to act by inducing antibodies that neutralize live JEV.

Mechanism of action

The mechanism of action of Japanese encephalitis (JE) vaccines is not well understood. Studies in animals have shown that the vaccine triggers the immune system to produce antibodies against Japanese encephalitis virus that are most often protective.

In other challenge studies in mice by a similar inactivated JE vaccine showed that almost all mice that had a Plaque Reduction Neutralization Test titre of at least ≥1:10 were protected from a lethal Japanese encephalitis virus challenge.

The World Health Organization consultation group recognizes a PRNT titer of ≥1:10 as being a reasonable correlate for protection.

Clinical studies

In a phase-I study, (N=20) the safety of this vaccine was established in healthy adult volunteers and the development proceeded to phase II/III study (N=456). The phase-II part of the phase-II/III study established single dose safety in healthy ≥ 1 to <3 year old Indian subjects which was closely monitored by an Independent Data Safety Monitoring Board.

The immunogenicity of the vaccine was further evaluated in healthy ≥1 to <3 year old Indian subjects of either gender in a multicentre, open label, parallel, randomized phase-II/III study. The objective was to evaluate both immunogenicity & safety of this vaccine administered intramuscularly to ≥1 to <3 year old healthy Indian children in 2-dose (0, 28 Day) schedule in comparison with a licensed mouse brain derived inactivated JE vaccine administered subcutaneously in 3-dose (0, 7 & 28 Day) schedule.

The primary end point was to assess whether proportion of subjects seroconverted ($PRNT_{50}$ ≥1:10) in both the groups at Day 56 were similar and JEEV® is non-inferior to the licensed Comparator JE vaccine. The study results revealed that the GMT levels increased from 9.7 at baseline to 217.9 by Day 56 with JEEV® and the vaccine demonstrated to be non-inferior to the licensed Comparator JE vaccine.

A multi-centre open randomized study (N=162) was conducted to compare the immunogenicity and safety of 6µg/0.5mL intramuscular dose of JEEV® vaccine in ≥18 to ≤49 year old adults, to demonstrate its non-inferiority with IXIARO®. A total of 99.07% in JEEV® group and 98.15% in IXIARO® group achieved seroprotection rates ($PRNT_{50}$≥1:10) at Day 56 with non-inferiority of JEEV® demonstrated. Both vaccines elicited strong immune response as seen by a large increase in anti-JEV neutralising antibodies and the high proportion of adults seroprotected. JEEV® vaccine was found to be safe and well tolerated. Injection site pain (reported in 44.7% in JEEV® vs. 54.2% in IXIARO®) was the most frequently reported local adverse event and fever (reported in 23.7% in JEEV® vs. 29.2% in IXIARO®) was the most frequently reported systemic adverse event in both groups with no statistically significant differences between groups. No serious adverse events were reported during this study in either of the groups.

A phase-IV post marketing safety study (N=432) was conducted in ≥18 to ≤49 year old adults to obtain additional safety information on 6µg/0.5mL intramuscular dose of JEEV® vaccine.

JEEV® vaccine continued to show similar clinical safety profile as seen in earlier studies. Injection site pain (16.9%) was the most frequently reported local adverse event and fever (2.08%) was the most frequently reported systemic adverse event. All reported adverse events were mild to moderate in their intensity, which resolved spontaneously.

In a safety and immunogenicity study (N=108) conducted in paediatric and adolescent population between ≥3 to <18 years of age, a 6µg/0.5mL intramuscular dose of JEEV® vaccine was found to be safe and highly immunogenic. Most of the reported adverse events were mild in nature and no serious adverse events were reported. The most common treatment emergent local adverse events were injection site pain (44.4%) and redness (7.41%) and the most common treatment emergent systemic adverse events were fever (4.63%) and myalgia (12.04%). Overall, 95.33% of subjects were found to be seroprotected by day 56 with ≥ 4-fold increase in titres above the seroprotection threshold defined ($PRNT_{50}$≥1:10).

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

Non-clinical toxicity data is limited

A 28-day repeat dose toxicity study of Japanese encephalitis vaccine (JEEV®) administered intramuscularly to Wistar rats in 3 occasions (1, 14 and 28 day) was found to be safe and immunogenic in animal studies. Non-clinical data reveal no special hazard for humans based on repeated dose toxicity in Mice.

In a similar reproductive and pre-/post-natal toxicity study with another JE vaccine, no vaccine-related effects were detected on reproduction, foetal weight, survival and development of the off-spring. However, incomplete ossification of parts of the skeleton was observed in the group receiving 2 doses, but not in the group receiving 3 doses. It is currently difficult to explain if this phenomenon is treatment related or not.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1. Phosphate buffer saline consisting of :
   - Sodium Chloride
   - Potassium dihydrogen phosphate
   - Disodium hydrogen phosphate
   - Water for injection
2. Aluminium as aluminum hydroxide hydrate
3. Thiomersal

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.