6.3 Shelf Life

6.4 Special precautions for storage

Store in a refrigerator at 2°C to 8°C (35°F to 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

Packaging for multi dose vials (5 doses):

- 5 ml suspension in 3 ml capacity glass vial (USP Type I glass) with stoppers (Grey Bromobenzylrubber) and 10 mm Aluminium seal.

Handling of multi dose vials:

- Once opened, hold dose 4 ml 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 6 weeks, provided that all of the following conditions are met:
  - the expiry date has not passed
  - the vaccine is stored under appropriate cold chain conditions
  - the vaccine vial septum has not been abraded in water
  - Assay 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.

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**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 0.5 ml contains:

- Purified Inactivated Japanese Encephalitis Virus Vaccine Strain (SA, 14-27).

Aluminium as aluminium hydroxide: 0.15 mg

Thiomersal: 0.005% w/v

Phosphate Buffer Saline: 0.1% produced in Vero cells.

The vaccine is formulated to be stored in a sterile glass vial.

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 homogeneous upon shaking.**

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

**JEEV** (0.5 mg in 0.5 ml) is indicated for active immunization against Japanese encephalitis in children and adults aged between 3 to 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 Pharmacology 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.

**Protocols**

The immunization schedule for JEEV should be based on official recommendations.

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

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

First dose: day 0
Second dose: 28 days after first dose

It is recommended that vaccine recipients receive second 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 1 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 of 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 residues (e.g. proteins, sugars).

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 individuals with known or suspected hypersensitivity to any constituent of the vaccine.

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**Manufactured by: Biological E. Limited**

Corporate Address: 18/1 & 3, Azamabad
Hyderabad, Telangana - 500 031, India.

Web: www.biological.com
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.

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

As with any other vaccine, vaccination with JEVIEV may not result in protection in all cases. JEVIEV will not protect against encephalitis caused by other micro-organisms.

4.5 Interactions with other medicinal products and other forms of interaction

Interactions with other medicinal products and other forms of interaction have not been performed on JEVIEV. When JEVIEV is administered concomitantly with injectable vaccines, they should be given with separate syringes at different injection sites. JEVIEV should not be mixed with any other vaccines 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 JEVIEV 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 JEVIEV on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The safety of the JEVIEV vaccine was assessed in a controlled clinical trial in 2 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 listed 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 (4.1%) and the most commonly reported systemic adverse reaction was pyrexia (1.6%). The most common adverse events reported were injection site swelling (5.3%), injection site erythema (5.3%), increased appetite (3.5%), diarrhea (2.2%) and vomiting (1.9%).

In a multicentre, open label, phase IV study conducted on Indian children (n=108) aged 2-3 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 (44.1%), redness (7.41%) and swelling (7.41%). The most common systemic adverse events were myalgia (12.94%), 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 adult Indians (n=162) aged 18 years to 45 years, comparing JEVIEV with IXARO, both the vaccines were found to have similar adverse event profile. Injection site pain (44.7%) in JEVIEV vs. 54.2% in IXARO was the most common local adverse event reported and fever (23.7% in JEVIEV vs. 23.2% in IXARO) 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

Pharmacodynamic group: Encephalitis Vaccines, ATC Code: J07B0A0

Japanese encephalitis is a disease caused by the mosquito-borne Japanese encephalitis virus (JEV). JEV is a cyroprotected purified inactivated vaccine that is shown to be effective in reducing 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 a 5-year survival study in mice by a similar method, JEVIEV showed all mice that had a Plaque Reduction Neutralization Test titre of at least 1:10 were protected from lethal Japanese encephalitis virus challenge.

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

Critical 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 trials (N=456). The phase I part of the phase III study established single dose safety in healthy 2 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 both genders in a multicentre, open label, randomized phase IIb study. The objective was to evaluate both immunogenicity & safety of this vaccine administered intramuscularly at 2 to 3 years 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, 21 Day) schedule.

The primary endpoint was to assess whether proportion of subjects seroconverted (PRNT ≥1:10) in both the groups at Day 56 were similar and JEVIEV is non-inferior to the licensed Comparator JE vaccine. The study results revealed the GMT levels increased from 9.7 at baseline to 217.8 by Day 56 with JEVIEV and the vaccine demonstrated to be non-Inferior to the licensed Comparator JE vaccine.

A multicentre open randomized study (N=162) was conducted to compare the immunogenicity and safety of IXARO intramuscular dose of JEVIEV vaccine in 2 to 6 year old adult, to demonstrate its non-inferiority with IXARO. A total of 99.0% in JEVIEV group and 88.1% in IXARO group achieved seroprotection rates (PRNT ≥1:10) at Day 56 with non-inferiority of JEVIEV demonstrated. Both vaccines elicited strong immune response as seen by a large increase in anti-JEV neutralizing antibodies and the high proportion of adults seroprotected. JEVIEV vaccine was found to be safe and well tolerated (Injection site pain reported in 44.7% in JEVIEV vs. 54.2% in IXARO) was the most frequently reported local adverse event and fever (reported in 23.7% in JEVIEV vs. 22.9% in IXARO) 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=442) was conducted in 218 to 549 year old adults to obtain additional safety information on JEVIEV in intramuscular dose of JEVIEV vaccines.

JEVIEV continued to show similar clinical safety profiles as seen in earlier studies. Injection site pain (16.8%) was the most frequently reported local adverse event and fever (20.8%) was the most frequently reported systemic adverse event. All reported adverse events were mild to moderate in intensity, which resolved spontaneously.

In a safety and immunogenicity study (N=180) conducted in peninsula and subtropical population between 23 to 18 years of age, a 66/0.5ml intramuscular dose of JEVIEV 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 4.4% in titre above the seroprotection threshold defined (PRNT ≥1:10).

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

Nonclinical toxicity data is limited.

A 28-day repeat dose toxicity study of Japanese encephalitis vaccine (JEVIEV) administered intramuscularly to Wistar rats in 3 occasions (1, 14 and 28 days) was found to be safe and immunogenic in animal studies. Non-clinical data was not specific hazard for humans based on repeated dose toxicity in Macaques.

In a similar reproductive and pre-pubertal toxicity study with another JE vaccine, no vaccine-related effects were detected on reproduction, fetal weight, survival and development of the offspring. However, microscopic identification of foci of the adipose tissue was observed in the group receiving 2 doses, but not in the group receiving 3 doses. It is currently difficult to explain this phenomenon as treatment-related or not.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1. Phosphate buffer saline consisting of:
   - Sodium O-nitrate
   - Potassium hydrogen phosphate
   - Dextrose hydrogen phosphate

2. Aluminium as aluminium hydroxide hydrate

3. Thiomersal

6.2 Incompatibilities

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