1. NAME OF THE MEDICINAL PRODUCT

Japanese Encephalitis Vaccine Inactivated (Adsorbed, Human) I.P. - 6 mcg/0.5 mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.5 mL of vaccine contains:

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

[1]produced in Vero cells

The vaccine is formalin inactivated

3. PHARMACEUTICAL FORM

Suspension for Injection.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

JE Vaccine is indicated for active immunization against Japanese encephalitis in Individuals from the age of ≥ 3 years to ≤ 49 years.

The vaccine should be used in children 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

Posology: The immunization schedule for JE Vaccine 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 vaccines who receive first dose of JE Vaccine should receive their 2nd dose of vaccination course with JE Vaccine only.

The vaccine has to be administered by a qualified healthcare professional. Immunization series should be completed at least a 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.

Method of administration: The vaccine should be administrated by intramuscular route. The preferred sites are anterolateral aspect of the thigh for children OR the deltoid muscle of upper arm for adults. Do not administer the vaccine intravenously, intradermally or subcutaneously.

For PFS, remove the prefilled syringe tip cap (syringe guard) by gently twisting it. Do not attempt to snap or pull the tip off as this may damage the syringe.

Two separate 25G needles (one 5/8” length & one 1” length) are supplied along with the prefilled syringe in the blister pack. The 5/8” needle is for use in deltoid muscle and 1” length needle is for use in anterolateral aspect of thigh in children ≥ 1 to ≤ 3years of age, Attach the selected needle to the prefilled syringe and remove the needle guard prior to administration.

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

4.4 Special Warning 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. JE Vaccine is an intramuscular vaccine and under no circumstances be administered intravenously.

As with any other vaccine, vaccination with JE Vaccine may not result in protection in all cases. JE Vaccine will not protect against encephalitis caused by other microorganisms. Like other intramuscular injections, this vaccine should not be administered to persons with thrombocytopenia, haemophilia or other bleeding disorders.

4.5 Drug interactions

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

4.6 Use in Special Populations (such as pregnant women, lactating women)

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 JE vaccine during pregnancy or lactation should be avoided. It is not known whether this vaccine is excreted in human milk.

4.7 Effect on Ability to Drive and Use Machines

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

4.8 Undesirable Effects

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, JE Vaccine with IXIARO®, both the vaccines were found to have similar adverse event profile. Injection site pain (44.7% in JE Vaccine vs. 54.2% in IXIARO®) was the most common local adverse event reported and fever (23.7% in JE Vaccine 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

This section is not applicable for this product as this vaccine is given by a registered medical practitioner.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Encephalitis vaccines ATC Code: J07BA02

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

5.1 Mechanism of Action

The mechanism of action of Japanese encephalitis vaccine is not well understood. Studies in animals have shown that vaccine triggers the immune system to produce antibodies against Japanese encephalitis virus (JEV) 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 titre of ≥1:10 as being a reasonable correlate for protection.

5.2 Pharmacodynamic Properties

In a phase-I study, (N=20) the safety of this vaccine was established in healthy adult volunteers.

A multi-centre open randomized study (N=162) was conducted to compare the immunogenicity and safety of 6µg/0.5mL intramuscular dose of JE Vaccine in ≥18 to ≤49 year old adults, to demonstrate its non-inferiority with IXIARO®. A total of 99.07% in JE Vaccine group and 98.15% in IXIARO® group achieved seroprotection rates ($PRNT_{50}$ ≥1:10) at Day 56 with non-inferiority of JE Vaccine 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. JE Vaccine was found to be safe and well tolerated. Injection site pain (reported in 44.7% in JE Vaccine vs. 54.2% in IXIARO®) was the most frequently reported local adverse event and fever (reported in 23.7% in JE vaccine 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 JE vaccine. JE 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 JE 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 y 56 with ≥ 4-fold increase in titres above the seroprotection threshold defined ($PRNT_{50}$≥1:10).

5.3 Pharmacokinetic Properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.4 Preclinical Safety Data

Non clinical toxicity data is limited.

A 28-day repeat dose toxicity study of Japanese Encephalitis Vaccine (JE vaccine) administered intramuscularly to wistar rats in 3 occasions (1, 14 & 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

received two doses, but not in the group received 3 doses. It is 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
2. Aluminium as aluminium hydroxide hydrate

6.2 Incompatibilities

JE vaccine must not be mixed with other medicinal products.

6.3 Shelf Life

3 years

6.4 Special Precautions for Storage

The vaccine should be store in a refrigerator at temperature between 2°C to 8°C. 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.

6.5 Nature and Contents of Container

- 0.5 ml of JE vaccine filled in 3 ml USP type I glass vial with bromobutyl rubber stopper and sealed with aluminum flip off seal.
- 0.5 ml of JE Vaccine is filled in Pre-filled syringe of USP Type I glass barrel, Stoppered with rubber stopper and fixed with plunger rod.

6.6 Special Precautions for Disposal

Discard if the vaccine has been frozen as per the approved procedures.

7. MARKETING AUTHORISATION HOLDER

Biological E. Limited

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8. MARKETING AUTHORISATION NUMBER(S)

MF-456/2011

9. DATE OF FIRST AUTHORISATION

05.11.2011