1. NAME OF THE MEDICINAL PRODUCT

Japanese Encephalitis Vaccine Inactivated (Adsorbed, Human) I.P. - 3 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]	:	3 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.

Appearance of the vaccine is a clear liquid with a white precipitate. A white cloudy liquid suspension forms upon agitation.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Japanese Encephalitis Inactivated Vaccine is indicated for active immunization against Japanese Encephalitis in children (between ≥ 1 to < 3 years of age).

The vaccine should be used in children 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 residing in areas where JE is endemic or epidemic.

JE vaccine should also be considered for short-term (<1 month) travellers whose itinerary or activities might increase their risk for exposure to JE virus. JE vaccine is not recommended for short-term travellers whose visit will be restricted to urban areas.

4.2 Posology and Method of Administration

Posology: The immunization schedule for Japanese Encephalitis Inactivated Vaccine should be based on official recommendations. 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 vaccines who received first dose of BE's Japanese Encephalitis Inactivated Vaccine should receive their second dose of vaccination course with BE's Japanese Encephalitis Inactivated Vaccine 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, homogenous suspension. Don't administer if particulate matter remains following shaking or if discoloration is observed.

Method of administration:

The vaccine should be administered by intramuscular route. The preferred site is anterolateral aspect of the thigh for children. 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 other 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 individuals with known or suspected hypersensitivity to any constituent of vaccine. 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. Japanese Encephalitis Inactivated Vaccine is an intramuscular vaccine and under no circumstances be administered intravenously.

As with any other vaccine, vaccination with Japanese Encephalitis Inactivated Vaccine may not result in protection in all cases.

Japanese Encephalitis Inactivated 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 Japanese Encephalitis Inactivated Vaccine. When Japanese Encephalitis Inactivated Vaccine is administered concomitantly with other injectable vaccines, they should be given with separate syringes at different injection sites. Japanese Encephalitis Inactivated Vaccine should not be mixed with any other vaccine in the same vial.

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

Not Applicable

4.7 Effect on Ability to Drive and Use Machines

Not Applicable

4.8 Undesirable Effects

The safety of the Japanese Encephalitis Inactivated Vaccine was assessed in a controlled clinical trials in ≥1 to <3 years old healthy Indian children. Adverse events usually occur within the first three days after vaccination and are usually mild or occasionally moderate in intensity and disappear within a few days. No increase in the number of adverse events reported was noted between first and second doses.

The most frequently reported local adverse reactions were injection site pain (10.86%), injection site erythema (2.99%) and injection site swelling (2.26%) and the most commonly reported systemic adverse reaction was pyrexia (14.3%). The other vaccine related adverse events reported were injection site tenderness (1.27%), injection site pruritus (0.63%), injection site induration (0.36%), skin rash (0.36%). decreased appetite (3.07%). Crying (2.08%). somnolence (1.81%). generalized rash (0.81%) and vomiting (0.18%)

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). Japanese Encephalitis Inactivated 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, the safety of Japanese Encephalitis Inactivated Vaccine was established in healthy adult volunteers and the development proceeded to phase II/III study. The phase II part of 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 established in healthy ≥1 to <3 year old Indian subjects of either gender in a multicentre, open label, parallel, randomized phase II/III study.

The safety of the vaccine was further established in a phase IV study. A Multi-centric open label non-interventional post marketing Surveillance study was conducted to evaluate safety and tolerability of BE's inactivated vero cell derived Japanese Encephalitis Inactivated Vaccine in ≥1 to <3 year old healthy children in a two dose schedule.

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 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

Japanese Encephalitis Inactivated 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

- Single dose Vial of 0.5 mL
- Single dose Pre-filled Syringe of 0.5 mL

0.5 mL suspension filled in 3 mL glass vial (USP type 1 glass vial) and closed with stoppers (Grey Bromobutyl rubber) and aluminum flip off seal.

0.5 mL suspension 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)

License Number: 01/RR/AP/2006/V/R

9. DATE OF FIRST AUTHORISATION

04.04.14