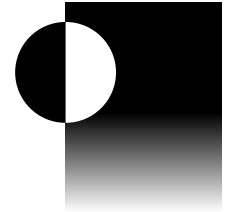


# Japanese Encephalitis Virus Vaccine Inactivated

## JE-VAX®

*R<sub>x</sub> only*



*CAUTION: Federal (USA) law prohibits dispensing without prescription.*

### DESCRIPTION

JE-VAX®, Japanese Encephalitis Virus Vaccine Inactivated, is a sterile, lyophilized vaccine for subcutaneous use, prepared by inoculating mice intracerebrally with Japanese encephalitis (JE) virus, “Nakayama-NIH” strain, manufactured by The Research Foundation for Microbial Diseases of Osaka University (“BIKEN®”). Infected brains are harvested and homogenized in phosphate buffered saline, pH 8.0. The homogenate is centrifuged and the supernatant inactivated with formaldehyde, then processed to yield a partially purified, inactivated virus suspension. This is further purified by ultra-centrifugation through 40% w/v sucrose. The suspension is then lyophilized in final containers and sealed under dry nitrogen atmosphere. Thimerosal (mercury derivative) is added as a preservative to a final concentration of 0.007%. The diluent, Sterile Water for Injection, contains no preservative. Each 1.0 mL dose contains approximately 500 µg of gelatin, less than 100 µg of formaldehyde, less than 0.0007% v/v Polysorbate 80, and less than 50 ng of mouse serum protein. No myelin basic protein can be detected at the detection threshold of the assay (< 2 ng/mL). Prior to reconstitution, the vaccine is a white caked powder, and after reconstitution the vaccine is a colorless transparent liquid. The potency of JE vaccine is determined by immunizing mice with either the test vaccine or the JE reference vaccine. Neutralizing antibodies are measured in a plaque neutralization assay performed on sera from the immunized mice. The potency of the test vaccine must be no less than that of the reference vaccine.

### CLINICAL PHARMACOLOGY

Japanese encephalitis (JE), a mosquito-borne arboviral Flavivirus infection, is the leading cause of viral encephalitis in Asia.

Infection leads to overt encephalitis in 1 of 20 to 1000 cases. Encephalitis, usually is severe, resulting in a fatal outcome in 25% of cases and residual neuropsychiatric sequelae in 50% of cases. JE acquired during the first or second trimesters of pregnancy may cause intrauterine infection and miscarriage. Infections that occur during the third trimester of pregnancy have not been associated with adverse outcomes in newborns.<sup>1</sup>

The virus is transmitted in an enzootic cycle among mosquitoes and vertebrate amplifying hosts, chiefly domestic pigs and, in some areas, wild Ardeid (wading) birds. Viral infection rates in mosquitoes range from < 1% to 3%. These species are prolific in rural areas where their larvae breed in ground pools and flooded rice fields. Thus all elements of the transmission cycle are prevalent in rural areas of Asia and human infections occur principally in this setting. Because vertebrate amplifying hosts and agricultural activities may be situated within and at the periphery of cities, human cases occasionally are reported from urban locations.<sup>1</sup>

JE virus is transmitted seasonally in most areas of Asia. The seasonal patterns of viral transmission are correlated with the abundance of vector mosquitoes and of vertebrate amplifying hosts. Although the abundance of vector mosquitoes fluctuates with the amount of rainfall, and with the impact of the rainy season, in some tropical locations, irrigation associated with agricultural practices is a more important factor affecting vector abundance, and transmission may occur year-round. Thus the periods of greatest risk for JE viral transmission vary regionally and within countries, and from year to year.<sup>1</sup>

In areas where JE is endemic, annual incidence ranges from 1 to 10 per 10,000 people. Cases occur primarily in children under 10 years of age. Seroprevalence studies in these endemic areas indicate nearly universal exposure by adulthood (calculating from a ratio of asymptomatic to symptomatic infections of 200 to 1, approximately 10% of the susceptible population is infected per year). In addition to children < 10 years, an increase in JE incidence has been observed in the elderly.<sup>1</sup>

Challenge experiments in passively protected mice have defined the levels of neutralizing antibody that may be protective for humans.<sup>2</sup> Mice passively immunized to achieve a neutralizing antibody titer of ≥ 1:10 were protected from a JE virus challenge of 10<sup>5</sup>LD<sub>50</sub>, a viral dose thought to be transmitted by an infected mosquito.<sup>2</sup>

The efficacy of the BIKEN Nakayama-NIH strain Japanese Encephalitis Virus Vaccine Inactivated was demonstrated in a placebo-controlled, randomized clinical trial in Thai children, sponsored by the US Army.<sup>3</sup> In this trial, children between 1 and 14 years of age received BIKEN monovalent Nakayama-NIH strain (n = 21,628) or a bivalent vaccine containing the Nakayama-NIH and Beijing JE virus strains (n = 22,080) or tetanus toxoid as a placebo (n = 21,516). Immunization consisted of two (2) subcutaneous 1.0 mL doses of vaccine, *except in children under 3 years of age who received two 0.5 mL doses*. One case (5 cases/100,000) of JE occurred in the monovalent vaccine group, one case (5 cases/100,000) in the bivalent vaccine group, and 11 cases (51 cases/100,000) in the placebo group. The observed efficacy of both monovalent and bivalent vaccines was 91% (95% confidence interval, 54% to 98%). Side effects of vaccination, including headache, sore arm, rash, and swelling were reported at rates similar to those in the placebo group, usually less than 1%. Symptoms did not increase after the second dose. It should be noted that a schedule of two doses, separated by seven days, as employed in this trial, may be appropriate for use in residents of endemic or epidemic areas, where pre-existing exposure to Flaviviruses may contribute to the immune response.<sup>3</sup>

A three-dose vaccination schedule is recommended for US travelers and military personnel, based on the Centers for Disease Control and Prevention (CDC) experience and on a controlled immunogenicity trial performed in US military personnel.<sup>4,5</sup> The CDC experience demonstrated that neutralizing antibody was produced in fewer than 80% of vaccinees following two doses of vaccine in US travelers and antibody levels declined substantially in most vaccinees within six months. The US Army studied the immunogenicity of JE-VAX in 538 volunteers. Two three-dose regimens were evaluated (Day 0, 7, and 14 or Day 0, 7, and 30). All vaccine recipients demonstrated neutralizing antibodies at 2 months and 6 months after initiation of vaccination. The schedule of Day 0, 7, and 30 produced higher antibody responses than the Day 0, 7, and 14 schedule. Two hundred and seventy-three of the original study participants were tested at 12 months post-vaccination and there was no longer a statistical difference in antibody titers between the two vaccination regimens.<sup>5</sup>

The full duration of protection is unknown. Of US Army volunteers completing a three-dose regimen, 252 agreed to receive a booster dose of vaccine one year after the primary series. All boosted participants still had antibody 12 months after the booster. Protective levels of neutralizing antibody persisted for 24 months (2 years) in all 21 persons who had not received a booster.<sup>5</sup> Definitive recommendations cannot be given on the timing of booster doses at this time.

## INDICATIONS AND USAGE

JE-VAX is indicated for active immunization against JE for persons one year of age and older. For recommended primary immunization series see **DOSAGE AND ADMINISTRATION** section.

JE-VAX should be considered for use in persons who plan to reside in or travel to areas where JE is endemic or epidemic during a transmission season. ***JE-VAX is NOT recommended for all persons traveling to or residing in Asia.*** The incidence of JE in the location of intended stay, the conditions of housing, nature of activities, duration of stay, and the possibility of unexpected travel to high-risk areas are factors that should be considered in the decision to administer vaccine. In general, vaccine should be considered for use in persons spending a month or longer in epidemic or endemic areas during the transmission season, especially if travel will include rural areas. Depending on the epidemic circumstances, vaccine should be considered for persons spending less than 30 days whose activities, such as extensive outdoor activities in rural areas, place them at particularly high risk for exposure.<sup>1</sup>

*In all instances, travelers are advised to take personal precautions to reduce exposure to mosquito bites. (See INFORMATION FOR PATIENTS section.)*

Current CDC advisories should be consulted with regard to JE epidemicity in specific locales.<sup>1</sup>

The decision to use JE-VAX should balance the risks for exposure to the virus and for developing illness, the availability and acceptability of repellents and other alternative measures, and the side effects of vaccination. Assessments should be interpreted cautiously because risk can vary within areas and from year to year and available data are incomplete. Estimates suggest that risk of JE in highly endemic areas during the transmission season can reach 1 per 5,000 per month of exposure; risk for most short-term travelers may be 1 per million or less. Although JE vaccine is reactogenic, rates of serious allergic reactions (generalized urticaria and/or angioedema) are low (approximately 1-104 per 10,000).<sup>1</sup>

Advanced age may be a risk factor for developing symptomatic illness after infection. JE acquired during pregnancy carries the potential for intrauterine infection and fetal death. These factors should be considered when advising elderly persons and pregnant women who plan visits to JE endemic areas.

There are no data on the safety and efficacy of JE vaccine in infants under one year of age. Whenever possible, immunization of infants should be deferred until they are one year of age or older.<sup>1</sup>

#### **Research laboratory workers:**

Laboratory acquired JE has been reported in 22 cases. JE virus may be transmitted in a laboratory setting through needle sticks and other accidental exposures. Vaccine-derived immunity presumably protects against exposure through these percutaneous routes. Exposure to aerosolized JE virus, and particularly to high concentrations of virus, such as may occur during viral purification, potentially could lead to infection through mucous membranes and possibly directly into the central nervous system through the olfactory mucosa. It is unknown whether vaccine-derived immunity protects against such exposures, but immunization is recommended for all laboratory workers with a potential for exposure to infectious JE virus.<sup>1</sup>

As with any vaccine, vaccination with JE-VAX may not result in protection in all individuals. Long-term protection, as demonstrated by persistence of neutralizing antibody for more than two years, has not yet been shown.

#### **CONTRAINDICATIONS**

Adverse reactions to a prior dose of JE vaccine manifesting as generalized urticaria and angioedema are considered to be contraindications to further vaccination.

Patients who develop allergic or unusual adverse events after vaccination should be reported through the Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.<sup>1</sup>

JE vaccine is produced in mouse brains and should not be administered to persons with a proven or suspected hypersensitivity to proteins of rodent or neural origin. ***HYPERSENSITIVITY TO THIMEROSAL IS A CONTRAINDICATION TO VACCINATION.***<sup>1</sup>

#### **WARNINGS**

**Adverse reactions to JE vaccine manifesting as generalized urticaria or angioedema may occur within minutes following vaccination. A possibly related reaction has occurred as late as 17 days after vaccination. Most reactions occur within 10 days with the majority occurring within 48 hours.**<sup>1</sup> (See ADVERSE REACTIONS section)

**Vaccinees should be observed for 30 minutes after vaccination and warned about the possibility of delayed generalized urticaria, often in a generalized distribution or angioedema of the extremities, face and oropharynx, especially of the lips.**<sup>1</sup>

**Vaccinees should be advised to remain in areas where they have ready access to medical care for 10 days after receiving a dose of JE vaccine. Vaccinees should be instructed to seek medical attention immediately upon onset of any reaction.**<sup>1</sup>

***Persons should not embark on international travel within 10 days of JE-VAX immunization because of the possibility of delayed allergic reactions.***<sup>1</sup>

**Persons with a past history of urticaria after hymenoptera envenomation, drugs, physical or other provocations, or of idiopathic cause appear to have a greater risk of developing reactions to JE vaccine (relative risk 9.1, 95% confidence interval 1.8 to 50.9).<sup>6</sup> This history should be considered when weighing risks and benefits of the vaccine for an individual patient. When patients with such a history are offered JE vaccine, they should be alerted to their increased risk for reaction and monitored appropriately. There are no data supporting the efficacy of prophylactic antihistamines or steroids in preventing JE vaccine-related allergic reactions.**<sup>1</sup>

Another case control study consisting of 5 cases and 15 controls identified an increased risk of hypersensitivity reactions to JE vaccine in individuals who had unusual alcohol consumption during the two days following vaccination (p=0.005).<sup>7</sup> **Recipients should be advised to avoid more than the usual alcohol intake during the 48 hours following JE vaccination.**

In the same study an increased risk for hypersensitivity reactions was seen in individuals who received other vaccines within the 7-day period prior to receipt of JE vaccine. **Where possible JE vaccine should be administered concurrently with other vaccines.**<sup>7</sup>

**Epinephrine and other medications and equipment to treat anaphylaxis should be available at vaccine administration centers.**

## PRECAUTIONS

### GENERAL

Epinephrine Injection (1:1000) must be immediately available should an acute anaphylactic reaction occur due to any component of the vaccine.

Prior to injection of any vaccine, all known precautions should be taken to prevent adverse reactions. This includes a review of the patient's history with respect to possible sensitivity to this vaccine, a similar vaccine or allergic disorders in general (see **CONTRAINDICATIONS** section).

A separate, sterile syringe and needle or a disposable unit should be used for each patient to prevent transmission of infectious agents from person to person. Needles should not be recapped and should be disposed of according to biohazard waste guidelines.

Although substantial neutralizing antibody titers are elicited by JE-VAX in more than 90% of US travelers without history of prior JE immunization or of prior exposure to JE, the precise relationship between antibody level and efficacy has not been established even though these titers persisted for at least two years after immunization.<sup>8</sup>

The decision to administer JE vaccine should balance the risks for exposure to the virus and for developing illness, the availability and acceptability of repellents and other alternative protective measures, and the side effects of vaccination.

### INFORMATION FOR PATIENTS

Patients should be advised of the following:

- JE-VAX is given to provide immunization against Japanese encephalitis virus.
- A three-dose immunizing series should be completed, except in unusual circumstances. (See **CONTRAINDICATIONS** and **DOSAGE AND ADMINISTRATION** sections)
- JE-VAX should be given to a pregnant woman only if, in the opinion of a physician, withholding the vaccine entails even greater risk.
- Any adverse events following JE-VAX should be reported through the Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967 after contacting the physician immediately.
- If the patient has a past history of urticaria (hives) (following hymenoptera envenomation, drugs, physical or other provocation or of idiopathic origin), adverse effects are more likely.
- Adverse events consisting of arm soreness and local redness can occur shortly after vaccination.
- Adverse events consisting of headache, rash, edema and generalized urticaria or angioedema may occur shortly after vaccination or up to 17 days (usually within 10 days) following vaccination.
- International travel should not be initiated within 10 days of JE-VAX vaccination because of the possibility of delayed adverse reactions. Patients should be instructed to seek medical attention immediately upon onset of any adverse reaction.
- Personal precautions should be taken to avoid exposure to mosquito bites by the use of insect repellents, and protective clothing. Avoiding outdoor activity, especially during twilight periods and in the evening, will reduce risk even further.

**DRUG INTERACTIONS**

There are no data on the effect of concurrent administration of other vaccines, drugs (e.g. chloroquine, mefloquine) or biologicals on the safety and immunogenicity of JE vaccine.

**CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY**

No studies have been performed to evaluate carcinogenicity, mutagenic potential, or impact on fertility.

**PREGNANCY****REPRODUCTIVE STUDIES - PREGNANCY CATEGORY C**

Animal reproduction studies have not been conducted with Japanese Encephalitis Virus Vaccine. It is not known whether Japanese Encephalitis Virus Vaccine can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Pregnant women who must travel to an area where risk of JE is high should be immunized when the theoretical risks of immunization are outweighed by the risk of infection to the mother and developing fetus. Japanese Encephalitis Virus Vaccine should be given to a pregnant woman only if clearly needed.

**NURSING MOTHERS**

It is not known whether JE-VAX is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when JE-VAX is administered to a nursing woman.

**PEDIATRIC USE**

*SAFETY AND EFFECTIVENESS OF JE-VAX IN INFANTS UNDER ONE YEAR OF AGE HAVE NOT BEEN ESTABLISHED.* (See **DO dosage AND ADMINISTRATION** section.)

**ADVERSE REACTIONS**

JE vaccine is associated with a moderate frequency of local and mild systemic adverse effects.<sup>3,4,5,9,10,11,12</sup> Tenderness, redness, swelling and other local effects have been reported in about 20% of vaccinees (< 1% to 31%). Systemic side effects, principally fever, headache, malaise, rash, and other reactions, such as chills, dizziness, myalgia, nausea, vomiting and abdominal pain have been reported in approximately 10% of vaccinees.

In a study conducted by the CDC less than 5% of the 1,756 US travelers immunized with a three-dose regimen of the vaccine reported headache, flu-like symptoms, fever, and other systemic complaints. Hives and facial swelling were reported in 0.2% and 0.1% of vaccinees, respectively. Local soreness occurred in 5.9% and local redness in 2.9%. There was no increase in the number or severity of reactions with increasing numbers of doses.<sup>8</sup>

The US Army studied 4,034 personnel from 1987 to 1989.<sup>11</sup> Using a two- or three-dose regimen of JE vaccine, arm soreness was described in 22.7%, local redness in 4.8%, headache in 15.2%, and a febrile episode in 5.5%. In another trial evaluating the safety and immunogenicity of a three-dose immunizing series (Day 0, 7, and 30 or Day 0, 7, and 14), performed in 538 adult volunteers in 1990, the Army determined that local soreness and redness occurred in 21% of vaccinees after the first dose, then decreased with subsequent injections ( $p < 0.0001$ , Chi-square for downward trend). Systemic symptoms including feverishness, headache and rash occurred in 5% of vaccinees after the first dose, then decreased with subsequent injections ( $p < 0.001$ , Chi-square for downward trend).<sup>5</sup> Participants who received the third dose on Day 14 reported more side effects than those who received the injection on Day 30. Among these volunteers, 252 received a booster injection of vaccine one year after receiving the first dose of the primary series. Side effects reported after the booster injection included local symptoms of soreness (24.5%) and redness (6.1%) at the injection site and systemic complaints of headache (4.9%), fever (1.6%), and rash (0.8%). Less than 1% of all reported symptoms was graded as severe. No generalized urticaria or anaphylaxis was reported.

Since 1989, an apparently new pattern of adverse reactions has been reported among vaccinees in Europe, North America, and Australia.<sup>12,13,14</sup> The reactions have been characterized by urticaria, often in a generalized distribution, or angioedema of the extremities, face, especially of the lips and oropharynx. Three vaccine recipients developed respiratory distress. Distress or collapse due to hypotension or other causes led to hospitalization in several cases. Most reactions were treated successfully with antihistamines or oral steroids; however some patients were hospitalized for parenteral steroid therapy. Three patients developed an erythema multiforme or erythema nodosum and some patients have had joint swelling. Some vaccinees complained of generalized itching without objective evidence of a rash.

An important feature of the reactions has been the interval between vaccination and onset of symptoms. Reactions after a first vaccine dose occurred after a median of 12 hours after immunization (88% of reactions occurred within 3 days). The interval between administration of a second dose and onset of symptoms generally was longer, (median 3 days and possibly as long as 2 weeks). Reactions have occurred after a second or third dose, when preceding doses were received uneventfully.

Between November 1991 and May 1992, the US Navy immunized 35,253 US personnel (marines, other military and dependents) with JE-VAX on Okinawa. The overall reaction rate, 62.4 per 10,000 vaccinees (95% confidence interval 54.2 to 70.6) includes persons reporting urticaria, angioedema, generalized itching and wheezing. The reaction rate per 10,000 vaccinees was 26.7 (95% confidence interval 21.3 to 32.1), 30.8 (95% confidence interval 24.6 to 37.0) or 12.2 (95% confidence interval 7.9 to 16.5) after the first, second or third dose, respectively.<sup>6</sup> These reactions were generally mild to moderate in severity. Nine out of 35,253 persons immunized were hospitalized (2.6 per 10,000 vaccinees) primarily to allow administration of intravenous steroids for refractory urticaria. None of these reactions were considered life-threatening.

A case-control study conducted as part of the JE immunization campaign in Okinawa found that persons developing these reactions after JE vaccination were more likely to have had a past history of urticaria after hymenoptera envenomation, drugs, physical or other provocations or of idiopathic origins (relative risk 9.1, 95% confidence interval 1.8 to 50.9).<sup>6</sup> The vaccine constituents responsible for these adverse reactions have not been identified.

Other serious adverse events reported following vaccination include (1) one case of Guillain-Barré syndrome after JE vaccination has been reported in the United States since 1984 (this patient was diagnosed as having mononucleosis three weeks before the onset of weakness); (2) one case of urticaria, hepatitis and respiratory failure one week after dose 2 (this person showed effusion and infiltrate on chest x-ray and eosinophilia); (3) one case of respiratory and renal failure one week after a dose (this 26-month-old male had infiltrate on chest x-ray and acid fast bacilli in sputum); and (4) one case of newly diagnosed hypertension in a young adult male presenting with a headache several hours after receiving dose one. The relationship of JE-VAX to the etiology of these adverse events is unknown.

Optic neuritis has been reported for one patient. In addition to JE-VAX, this patient concurrently received a number of other vaccines.<sup>15</sup>

Fatal myocarditis has been reported in a patient who had recently been given meningococcal vaccine and at least one dose of JE vaccine. Any causal role for the vaccines is unclear.<sup>15</sup>

Sudden death occurred approximately 60 hours after receiving the first dose of JE vaccine in a 21-year-old US military person with a history of recurrent hypersensitivity and an episode of possible anaphylaxis. This person also received the third dose of plague vaccine approximately 12 to 15 hours prior to the death. There was no evidence of urticaria or angioedema. Cause of death was not established at autopsy.

Surveillance of JE vaccine related complications in Japan from 1965 to 1973 disclosed neurologic events (primarily encephalitis, encephalopathy, seizures, and peripheral neuropathy) in 1 to 2.3 per million vaccinees.<sup>16,17</sup> Very rarely, deaths occurred with vaccine-associated encephalitis. Between 1987 and 1989, two cases of neurologic dysfunction were reported from Japan; one of these was a transverse myelitis, while the second included seizures, cranial nerve paresis, cerebellar ataxia, and behavior disorder.<sup>17</sup> In 1992, two cases of acute disseminated encephalomyelitis were reported from Japan; one occurred 14 days after the second dose and the second occurred 17 days after a booster dose of JE vaccine. Both cases recovered.<sup>18</sup> One case of Bell's Palsy was reported from Thailand.

### **Reporting of Adverse Events**

The National Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act of 1986, requires physicians and other health-care providers who administer vaccines to maintain permanent vaccination records and to report occurrences of certain adverse events to the US Department of Health and Human Services. Reportable events include those listed in the Act for each vaccine and events specified in the package insert as contraindications to further doses of that vaccine.<sup>19,20,21</sup>

Reporting by parents and patients of all adverse events occurring after antigen administration should be encouraged. Adverse events following immunization with vaccine should be reported by the health-care provider to the US Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS). Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 1-800-822-7967.<sup>19,20,21</sup>

**Health-care providers also should report these events to the Director of Scientific and Medical Affairs, Aventis Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call 1-800-822-2463.**

### **DOSAGE AND ADMINISTRATION**

Parenteral drug products should be inspected visually for extraneous particulate matter and/or discoloration prior to administration whenever solution and container permit. If either of these conditions exist, the vaccine should not be administered.

For persons 3 years of age and older, a single dose is 1.0 mL of vaccine. *For children 1 year to 3 years of age, a single dose is 0.5 mL of vaccine.* (See PRIMARY IMMUNIZATION SCHEDULE below.)

**Single-Dose vial of lyophilized vaccine:** Remove plastic tab of flip-off cap. DO NOT REMOVE RUBBER STOPPER. Cleanse stopper with a suitable disinfectant. Reconstitute only with the supplied 1.3 mL of diluent (Sterile Water for Injection). Shake vial thoroughly. After reconstitution the vaccine should be stored between 2°– 8°C (35° – 46°F) and used within 8 hours. DO NOT FREEZE RECONSTITUTED VACCINE.

**10-Dose vial of lyophilized vaccine:** Remove plastic tab of flip-off cap. DO NOT REMOVE RUBBER STOPPER. Cleanse stopper with a suitable disinfectant. Reconstitute only with the supplied 11 mL of diluent (Sterile Water for Injection). Shake vial thoroughly. After reconstitution the vaccine should be stored between 2° – 8°C (35° – 46°F) and used within 8 hours. DO NOT FREEZE RECONSTITUTED VACCINE.

**The vaccine is to be given by subcutaneous administration only.**

A separate, sterile syringe and needle or a sterile disposable unit should be used for each patient to prevent transmission of infectious agents from person to person. Needles should not be recapped and should be disposed of according to biohazard waste guidelines.

### **SHAKE VIAL WELL.**

#### **PRIMARY IMMUNIZATION SCHEDULE<sup>1</sup>**

The recommended primary immunization series is three doses of 1.0 mL each for individuals > 3 years of age given subcutaneously on days 0, 7, and 30. *For children 1 to 3 years of age a series of three doses of 0.5 mL each should be given subcutaneously on days 0, 7, and 30.* An abbreviated schedule of days 0, 7, and 14 can be used when the longer schedule is impractical because of time constraints. (When it is impossible to follow one of the above recommended schedules, two doses given a week apart will induce antibodies in approximately 80% of vaccinees; however, this two-dose regimen should not be used except under unusual circumstances.) The last dose should be given at least 10 days before the commencement of international travel to ensure an adequate immune response and access to medical care in the event of delayed adverse reactions.

A booster dose of 1.0 mL (*0.5 mL for children from 1 to 3 years of age*) may be given after two years. In the absence of firm data on the persistence of antibody after primary immunization, a definite recommendation cannot be made on the spacing of boosters beyond two years.

There are no data on the safety and efficacy of JE vaccine in infants under one year of age. Whenever possible, immunization of infants should be deferred until they are one year of age or older.<sup>1</sup>

The skin at the site of injection first should be cleansed and disinfected. Shake vial thoroughly before each use. Cleanse top of rubber stopper of the vial with a suitable antiseptic and wipe away all excess before withdrawing vaccine.

When JE-VAX and any other vaccines are given concurrently, separate syringes and separate sites should be used.

### **HOW SUPPLIED**

Vial, Single Dose (3 per package) with vial of Diluent (3 per package) – Product No. 49281-680-30

Vial, 10 Dose with vial of Diluent – Product No. 49281-680-20

For persons 3 years of age and older, a single dose is 1.0 mL of vaccine. *For children 1 year to 3 years of age, a single dose is 0.5 mL of vaccine.* (See PRIMARY IMMUNIZATION SCHEDULE above.)

**STORAGE**

The vaccine should be stored between 2° – 8°C (35° – 46°F). DO NOT FREEZE. After reconstitution the vaccine should be stored between 2° – 8°C (35° – 46°F) and used within 8 hours. DO NOT FREEZE RECONSTITUTED VACCINE.

**REFERENCES**

1. Recommendations of the Advisory Committee on Immunization Practices (ACIP). Inactivated Japanese Encephalitis Virus Vaccine. MMWR 42: 1-15, 1993
2. Oya A. Japanese Encephalitis Vaccine. Acta Paediatr Jpn 30: 175-184, 1988
3. Hoke CH, et al. Protection Against Japanese Encephalitis by Inactivated Vaccines. N Eng J Med 319: 608-614, 1988
4. Poland JD, et al. Evaluation of the Potency and Safety of Inactivated Japanese Encephalitis Vaccine in US Inhabitants. J Infect Dis 161: 878-882, 1990
5. DeFraités RF. Immunogenicity and Safety of Japanese Encephalitis Vaccine (Inactivated: Nakayama/BIKEN) in U.S. Army Soldiers: Evaluation of Three Consecutively Manufactured Lots of Vaccine Administered in Two Dosing Regimens. April 30, 1991, and November 12, 1992. Unpublished Data, on file with BIKEN and with Walter Reed Army Institute of Research, Washington, DC
6. Berg WS. Systemic Reactions in U.S. Marine Corps Personnel Who Received Japanese Encephalitis Vaccine. Clin Infect Dis 24:265-266, 1997
7. Robinson P, et al. Australian Case-Control Study of Adverse Reactions to Japanese Encephalitis Vaccine. J Travel Med 2: 159-164, 1995
8. Unpublished data on file with “BIKEN” and CDC
9. Rojanasuphot S. et al. A field trial of Japanese encephalitis vaccine produced in Thailand. Southeast Asian J Trop Med Publ Health 20: 653-654, 1989
10. Rao Bhau LN, et al. Safety and efficacy of Japanese encephalitis vaccine produced in India. Indian J Med Res 88: 301-307, 1988
11. Sanchez JL, et al. Further Experience with Japanese Encephalitis Vaccine. Lancet 335: 972-973, 1990
12. Japanese Encephalitis Vaccine and Adverse Effects among Travelers. Canada Diseases Weekly Report. Vol. 17-32: 173-177, 1991
13. Andersen MM, et al. Side-Effects with Japanese Encephalitis Vaccine. Lancet 337: 1044, 1991
14. Ruff TA, et al. Adverse Reactions to Japanese Encephalitis Vaccine. Lancet 338: 881-882, 1991
15. Unpublished data on file with Aventis Pasteur Inc.
16. Kitaoka M. Follow-up on use of vaccine in children in Japan, in McD Hammon W, Kitaoka M, Downs WG eds. Immunization for Japanese encephalitis. Excerpta Medica, Amsterdam 275-277, 1972
17. Unpublished data on file with “BIKEN”
18. Ohtaki E, et al. Acute disseminated encephalomyelitis after Japanese B Encephalitis Vaccination. Pediatric Neurology Vol. 8 No. 2: 137-139, 1992
19. CDC. Vaccine Adverse Event Reporting System – United States. MMWR 39: 730-733, 1990
20. CDC. National Childhood Vaccine Injury Act. Requirements for permanent vaccination records and for reporting of selected events after vaccination. MMWR 37: 197-200, 1988
21. Food and Drug Administration. New Reporting Requirements for Vaccine Adverse Events. FDA Drug Bull 18(2), 16-18, 1988

Manufactured by:

**The Research Foundation for Microbial  
Diseases of Osaka University**

Suita, Osaka, Japan  
“BIKEN®”

Distributed by:

**Aventis Pasteur Inc.**

Swiftwater PA 18370 USA

1-800-VACCINE (1-800-822-2463)

Product Information  
as of February 1997

4345

**Aventis Pasteur**

 **Aventis**