YF-VAX®, Yellow Fever Vaccine, for subcutaneous use, is prepared by culturing the 17D-204 strain of yellow fever virus in living avian leukosis virus-free (ALV-free) chicken embryos. The vaccine contains sorbitol and gelatin as a stabilizer, is lyophilized, and is maintained in a refrigerated environment. No preservative is systemically included in the vaccine. The vaccine is supplied with a separate vial of sterile diluent, which contains Sodium Chloride Injection USP – without a preservative. YF-VAX is formulated to contain not less than 4.74 log\(_{10}\) plaque forming units (PFU) per 0.5 mL dose throughout the life of the product. Before reconstitution, YF-VAX is a pinkish color. After reconstitution, YF-VAX is a slight pink-brown suspension.

The vial stoppers for YF-VAX and diluent are not made with natural rubber latex.

**CLINICAL PHARMACOLOGY**

Yellow fever is an acute viral illness caused by a mosquito-borne flavivirus. Most yellow fever virus infections are asymptomatic. In those individuals who develop disease, the clinical spectrum ranges from nonspecific flu-like illness with fever, malaise, prostration, headache, photophobia, generalized arthralgia and myalgia, nausea, and/or vomiting to potentially life-threatening panencephalitic disease, most prominently involving the liver, kidneys, gastrointestinal tract, and brain, with recrudescing fever, jaundice, renal failure, severe hemorrhage due to thrombocytopenia, and shock. (1) The case-fatality rate of yellow fever varies widely in different studies but is typically 20% or higher. Jaundice or other gross evidence of severe liver disease is an important marker of mortality.

Two live, attenuated yellow fever vaccines, strains 17D-204 and 17DD, were derived in parallel in the 1930s. Historical data suggest that these “17D vaccines” have identical safety and immunogenicity profiles. Vaccination with 17D strain vaccines is predicted to elicit an immune response identical in quality to that induced by wild-type infection. This response is elicited by different epitopes derived from the surface of virus in the dermis or other subcutaneous tissues near the injection site, with subsequent replication and spread of virus leading to the processing and presentation of viral antigens to the immune system, activation of the immune system resulting in viral failure and internal bleeding, leading to death. (See ADVERSE REACTIONS section.) Available evidence suggests that the occurrence of this syndrome may depend upon undefined host factors, rather than intrinsic virulence of the yellow fever strain 17D vaccine, based on characterization of vaccine viruses isolated from individuals with YEL-AVD. YEL-AVD has been reported to occur only after the first dose of yellow fever vaccine; there have been no reports of YEL-AVD following booster doses. (17) The decision to vaccinate individuals 60 years of age and older needs to weigh the risks and benefits of vaccination and the risk for exposure to yellow fever virus. (18) (19) (20) (21)

**WARNINGS**

**Severe Allergic Reactions**

Severe allergic reactions (e.g., anaphylaxis) may occur following the use of YF-VAX, even in individuals with no prior history of hypersensitivity to the vaccine components. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

**Yellow fever vaccine-associated viscerotropic disease**

Agreater than 60 years is a risk factor for yellow fever vaccine-associated viscerotropic disease (YEL-AVD) (14) which may manifest as an acute, self-limited systemic illness or as fulminant liver failure or encephalitis, also known as yellow fever vaccine-associated neurotropic disease (YEL-AND). (See ADVERSE REACTIONS section.) Because the yellow fever virus is propagated in chicken embryos, do not administer YF-VAX to anyone with a history of acute hypersensitivity to eggs or egg products due to a risk of anaphylaxis. Less severe or localized manifestations of allergy to eggs or to feathers are not contraindications to vaccine administration and do not usually warrant vaccine skin testing. (See PRECAUTIONS section, Testing for Hypersensitivity Reactions subsection.) Consider desensitization, if necessary, for people who are able to eat eggs or egg products may receive the vaccine. (14) (15)

**Individuals Less Than 9 Months of Age**

Vaccination with YF-VAX is contraindicated in infants less than 9 months of age due to the associated risk of death due to severe illness. (14) (17)

**Immunosuppressed Individuals**

Vaccination with YF-VAX, a live virus vaccine, is contraindicated in individuals with severe immunosuppression, including for example, those with acquired immunodeficiency syndrome (AIDS), leukemia, lymphoma, thymic disease, generalized malignancy, and patients who are undergoing drug therapy (e.g., alkylating agents, live virus vaccines, and antimitotics) or other immunosuppressive agents. 

**PRECAUTIONS**

**General**

Vaccination with YF-VAX may not protect 100% of individuals. Do not administer YF-VAX by intravascular, intramuscular, or intradermal routes. Use a separate, sterile syringe and needle for each patient to prevent transmission of blood borne infectious agents. Do not recap needles. Dispose of needles and syringes according to biohazard waste guidelines.

**Testing for Hypersensitivity Reactions**

If you administer YF-VAX to an individual with a history of hypersensitivity to egg or chicken protein, (See CONTRAINDICATIONS section.) However, if an individual is suspected of being an egg-sensitive individual, the following test can be performed before the vaccine is administered:

**Dermal test.** Place a drop of a 1:10 dilution of the vaccine in physiologic saline on a superficial scratch, prick, or puncture test. The test is read after 15 to 20 minutes. A positive test is a wheal (superficial bump) 3 mm larger than that of the saline control. Each vial of vaccine is accompanied with a鲎 Test Control Suspension. (See DOSAGE AND ADMINISTRATION section, Desensitization subsection.)

**Syncope**

Syncope can occur following or even before vaccination. Procedures should be in place to prevent falling and injury and to manage syncope.
Information for Patients

Prior to administration of YF-VAX, ask potential vaccinees or their parents or guardians about their recent health status and history of yellow fever vaccination. Inform potential vaccinees or their parents or guardians about the benefits and risks of immunization and potential for adverse reactions to YF-VAX administration. (See CONTRAINDICATIONS and ADVERSE REACTIONS sections.)

Drug Interactions

Data are limited in regard to the interaction of YF-VAX with other vaccines.

• Measles (Schwartz strain) vaccine, diphtheria and tetanus toxoids and whole cell pertussis vaccine (DTP), (22) Hepatitis A and Hepatitis B vaccines, (5) (14) (23) (24) meningococcal vaccine, Menomune® ACWY/135, and typhoid vaccine, Typhim Vi®, (5) (14) (23) have been administered with yellow fever vaccine at separate injection sites.

• The potential for interference between yellow fever vaccine and rabies or Japanese encephalitis vaccines has not been established. (14)

• In a prospective study, combination doses given 5 cc of commercially available immune globulin did not show interference in immunologic responses to the yellow fever vaccine. (14) (25) (26)

• Although chloroquine inhibits replication of yellow fever vaccine in vitro, it does not appear to affect adversely antibody responses to yellow fever vaccine among persons receiving chloroquine. (14) (27)

Patients on Corticosteroid Therapy

Oral Prednisone or other systemic corticosteroid therapy, depending on dose and duration of exposure, is associated with increased risk of adverse reactions in recipients of yellow fever vaccine. Studies have shown that corticosteroids have an immunosuppressive effect on recipients of yellow fever vaccine. Therefore, documentation of a protective antibody response is recommended before administration. Immediate hypersensitivity reactions, characterized by rash, urticaria, and/or asthma, occur principally among persons with histories of allergy to eggs or other substances contained in the vaccine. Documentation of a protective antibody response is recommended before administration. Immediate hypersensitivity reactions, characterized by rash, urticaria, and/or asthma, occur principally among persons with histories of allergy to eggs or other substances contained in the vaccine.

Additional information is available from local health departments, the Centers for Disease Control and Prevention (CDC), and WHO. Travel agencies, international airlines, and/or shipping lines may also have up-to-date information. The vaccination center should complete and submit an International Certificate of Vaccination and provide the certificate to the vaccinee. The immunization record should contain the date, lot number and manufacturer of the vaccine administered. Inform vaccinees that vaccination certificate cards are valid commencing 10 days after vaccination. (14)

Geriatric Use

There is an increased risk of severe systemic adverse reactions to YF-VAX in individuals 60 years of age and older. Monitor elderly individuals for signs and symptoms of yellow fever vaccine-associated viscerotropic disease, which typically occurs within 10 days post-vaccination. (See WARNINGS and ADVERSE REACTIONS sections.) (16) (31) ADVERSE REACTIONS

Data from Clinical Studies

Additional adverse events have been spontaneously reported during the post-marketing experience of YF-VAX worldwide. Because these events are voluntarily reported from a population of uncertain size, it is not possible to estimate their frequency reliably or establish a causal relationship to vaccine exposure. This list includes adverse events based on one or more of the following factors: severity, frequency of reporting, or strength of evidence for a causal relationship to YF-VAX.

• General disorders and administration site conditions
• Injection-site blisters
• Immune System Disorders (14)

• Immediately hypersensitivity reactions or anaphylaxis, characterized by rash and/or urticaria

• Nervous System Disorders (1) (32) (33) (34)

Isolated cases of Yellow Fever Vaccine-Associated Neurotropic Disease (YEL-AND), sometimes fatal, have been reported to occur within 30 days following vaccination with YF-VAX, and other yellow fever vaccines. (See WARNINGS section, Yellow fever vaccine-associated neurotropic disease subsection.) Age less than 9 months and congenital or acquired immunodeficiency have been identified as risk factors for this event. (See WARNINGS and CONTRAINDICATIONS sections.) Twenty-one cases of YEL-AND associated with all licensed 17D vaccines have been reported between 1952 and 2004. Eighteen of these cases were in children or adolescents. Fifteen of these cases occurred prior to 1990, thirteen of which occurred in infants 4 months of age or younger, and two of which occurred in infants six and seven months old. The incidence of vaccine-associated neurologic disease in infants less than 4 months old is estimated to be between 1 in 100,000 and 1 in 100,000 doses administered. (33) (34) (35) A study in Senegal (34) described two fatal cases of encephalitis possibly associated with 17D-204 vaccination among 67,325 children between the ages of 6 months and 2 years, for an incidence rate of 3 per 100,000. The incidence of YEL-AND in the United States is less than 1 in 1,100,000 doses administered. (17) (33) (34) (35) Other neurological complications have included Guillain-Barré syndrome (GBS), acute disseminated encephalomyelitis (ADEM), and bupar tal

• Infections and infestations

Isolated cases of Yellow Fever Vaccine-Associated Viscerotropic Disease YEL-AND, also referred to as “Febrile Multiple Organ-System Failure”, sometimes fatal, have been reported following YF-VAX and other yellow fever vaccines. (See WARNINGS section, Yellow fever vaccine-associated viscerotropic disease subsection.) In the majority of cases reported, the onset of signs and symptoms was within 10 days after vaccination, with signs specific to each vaccine and in some cases, specific to a single product. (17) (36) The pathophysiology and mechanisms of such reactions have not been established. In some individuals with YEL-AND a medical history of malnutrition or fever within the last 60 days has also been identified as a risk factor for this event. (9) During surveillance in the U.S. between 1996 and 1998, four individuals (ages 63, 67, 76, and 79) became severely ill 2 to 5 days after vaccination with YF-VAX vaccine. Three of these 4 subjects died. The
incidence rate for these serious adverse events was estimated at 1 per 400,000 doses of YF-VAX vaccine, based on the total number of doses administered in the U.S. civilian population during the surveillance period. (21) YEL-AVD has occurred after yellow fever vaccination in fewer than 1:100,000 U.S. vaccinees, (14) most commonly in individuals 60 years of age and older.

In a CDC analysis of data submitted to the Vaccine Adverse Events Reporting System (VAERS) in 2010 and 2011, the rate of systemic adverse events following vaccination was 2.5-fold higher in the 65 years or older age group (6.2 events per 100,000 doses of vaccine) compared to the 25 to 44 year-old age group (2.5 events per 100,000 doses of vaccine). (31)

**Reporting of Adverse Events**

To report SUSPECTED ADVERSE REACTIONS, contact the Pharmacovigilance Department, Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 at 1-800-822-2463 (1-800-VACCINE) or VAERS at 1-800-822-7976 or https://vaers.hhs.gov.

**DOSE AND ADMINISTRATION**

**Primary Vaccination**

Administer a single subcutaneous injection of 0.5 mL of reconstituted vaccine.

**Additional Dosing Information**

A single dose of yellow fever vaccine provides long-lasting protection to most healthy individuals. (See CLINICAL PHARMACOLOGY section.) However, an additional dose of yellow fever vaccine may be given to individuals who might not have had an adequate or sustained immune response to prior yellow fever vaccination and who continue to be at risk for exposure to yellow fever virus. Such individuals include women who were vaccinated during pregnancy, hematopoietic stem cell transplant recipients, and HIV-infected persons.

**Booster Vaccination**

A booster dose may be given to individuals who were last vaccinated against yellow fever at least 10 years prior and who are at increased risk for yellow fever disease either because of location and duration of travel or because of more consistent exposure to the virus. The incidence rate for these serious adverse events was estimated at 1 per 400,000 doses of vaccine, based on the total number of doses administered in the U.S. civilian population during the surveillance period. In the U.S., the booster dose of yellow fever vaccine is usually given to travelers who are at increased risk for yellow fever disease. The booster dose of yellow fever vaccine is given 10 years after the primary vaccination because of location and duration of travel or because of more consistent exposure to the virus. The booster dose of yellow fever vaccine is given 10 years after the primary vaccination because of location and duration of travel or because of more consistent exposure to the virus.

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Sanofi Pasteur Inc.

Swiftwater, PA 18370 USA

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