**DESCRIPTION**

**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 formulated with a sterile 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.**

**CLINICAL PHARMACOLOGY**

Yellow fever virus is a 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 fatal panensymic disease, most prominently involving the liver, kidneys, GI 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 associated with higher mortality rates. Two live, attenuated yellow fever vaccines, strains 17D-204 and 17DD, were derived in 208 adults who received YF-VAX. The seroconversion rate was 81% in one study involving 32 subjects and 97% to 100% in the other four studies. (1) (4) (5) (6) (7)

Vaccination with YF-VAX is also contraindicated in lactating women who are providing breastmilk to infants less than 9 months of age due to the potential for transmission of vaccine virus in breastmilk. (See PRECAUTIONS section, Nursing Mothers subsection.) 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.

**INDICATIONS AND USAGE**

**Vaccination with YF-VAX®**

**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**

Do not administer YF-VAX to an individual with a history of egg hypersensitivity to any component of the vaccine. (See CONTRAINDICATIONS section.) Because the yellow fever virus used in the production of this vaccine is propagated in chicken embryos, do not administer YF-VAX to individuals 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.) Generally, persons who are able to eat eggs or egg products may receive the vaccine. (14) (15)

**Laboratory Personnel**

Laboratory personnel who handle virulent yellow fever virus or concentrated preparations of the yellow fever vaccine virus strains may be at risk of exposure by direct or indirect contact or by aerosols. (14)

**CONTRAINDICATIONS**

**Hypersensitivity**

YF-VAX is contraindicated in anyone with a history of acute hypersensitivity reaction to any component of the vaccine. (See DESCRIPTION section.) Because the yellow fever virus used in the production of this vaccine 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.)

**INDICATIONS AND USAGE**

**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), human immunodeficiency virus (HIV) infection, or current or past treatment with agents that interfere with the immune system (e.g., corticosteroids, alkylating drugs, immunosuppressive drugs, or radiation therapy). Thymic disorders associated with abnormal immune cell function (e.g., myasthenia gravis, thymoma) may be an independent risk factor for the development of yellow fever vaccine-associated viscerotropic disease. (See WARNINGS subsection.)

**Severe Allergic Reactions**

Severe allergic reactions (e.g., anaphylaxis) may occur following the use of YF-VAX, 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**

Age greater than 60 years is a risk factor for yellow fever vaccine-associated viscerotropic disease (YEL-AVD) (14) which may manifest as non-specific multi-organ system failure or disseminated intravascular coagulation (DIC). 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 with YF-VAX and the risk for exposure to yellow fever virus. (18) (19) (20) (21)

**Yellow fever vaccine-associated neurotropic disease**

Age greater than 60 years and immunosuppression are risk factors for post-vaccinal encephalitis, also known as yellow fever vaccine-associated neurotropic disease (YEL-AND). (See ADVERSE REACTIONS section.) While the actual risk for contracting yellow fever during travel is probably low, variability in 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 fatal panensymic disease, most prominently involving the liver, kidneys, GI 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 associated with higher mortality rates. Two live, attenuated yellow fever vaccines, strains 17D-204 and 17DD, were derived in 208 adults who received YF-VAX. The seroconversion rate was 81% in one study involving 32 subjects and 97% to 100% in the other four studies. (1) (4) (5) (6) (7)

**INDICATIONS AND USAGE**

**Persons Living in or Traveling to Endemic Areas**

In two separate clinical trials of 17D-204 vaccines, 90% of subjects seroconverted within 32 days and never lower than 81%. There were no significant age-related differences in immuno- nogenicity. (1)

In 24 uncontrolled studies conducted world-wide between 1962 and 1997 evaluating neutralizing antibody responses to 17D vaccines among a total of 2,529 adults and 991 infants and children, the seroconversion rate was greater than 91% in all but two studies and never lower than 81%. There were no significant age-related differences in immuno- nogenicity. (1)

Five of these 24 studies were conducted in the US between 1962 and 1993 and included 208 adults who received YF-VAX. The seroconversion rate was 81% in one study involving 32 subjects and 97% to 100% in the other four studies. (1) (4) (5) (6) (7)

In 2001, YF-VAX was used as a control in a double-blind, randomized comparison trial with another 17D-204 vaccine, conducted at nine centers in the US. YF-VAX was administered to 725 adults 5 years old with a mean age of 38 years. Three hundred twelve of these subjects who received YF-VAX were evaluated serologically, and 99.3% of them seroconverted with a mean LNI of 2.21. The LNI was slightly higher among males compared to females and slightly lower among Hispanic and African-American subjects compared to others, but none were associated with differences in the immune response to the vaccine. There was no difference in mean LNI for subjects <40 years old compared to subjects ≥40 years old. Due to the small number of subjects (1.7%) with prior flavivirus immunity, it was not possible to draw conclusions about the role of this factor in the immune response to the vaccine.

For most healthy individuals, a single dose of yellow fever vaccine provides long-lasting protection. (9) (10) In controlled studies where the immune response to vaccination was evaluated, the small percentage of immunologically normal individuals who failed to develop an immune response to an initial vaccination typically did so upon re-vaccination. (11)

In two separate clinical trials of 17D-204 vaccines, 90% of subjects seroconverted within 10 days after vaccination. (12) and 100% of subjects seroconverted within 14 days. (1)

Thus, International Health regulations stipulate that the vaccination certificate for yellow fever is valid 10 days after administration of YF-VAX. (13)

**CLINICAL PHARMACOLOGY**

**Immunogenicity.**

The immunogenicity of the yellow fever vaccine virus strains may be at risk of exposure by direct or indirect contact or by aerosols. (14)

**INDICATIONS AND USAGE**

**Persons Living in or Traveling to Endemic Areas**

While the actual risk for contracting yellow fever during travel is probably low, variability of itineraries, behaviors and seasonal incidence of disease make it difficult to predict the actual risk for a given individual living in or traveling to a known endemic or epidemic area. Greater risk is associated with living in or traveling to areas of South America and Africa where yellow fever infection is officially reported at the time of travel and with traveling outside the urban areas of countries that do not officially report the disease but that lie in a yellow endemic zone.

**Persons Living Internationally Through Countries with Yellow Fever**

Some countries require an individual to have a valid International Certificate of Vaccination or Prophylaxis (ICVP) if the individual has been in countries either known or thought to harbor yellow fever virus. The certificate becomes valid 10 days after vaccination with YF-VAX. (13) (14)

**ADVERSE REACTIONS**

**INDICATIONS AND USAGE**

**Persons Living in or Traveling to Endemic Areas**

While the actual risk for contracting yellow fever during travel is probably low, variability of itineraries, behaviors and seasonal incidence of disease make it difficult to predict the actual risk for a given individual living in or traveling to a known endemic or epidemic area. Greater risk is associated with living in or traveling to areas of South America and Africa where yellow fever infection is officially reported at the time of travel and with traveling outside the urban areas of countries that do not officially report the disease but that lie in a yellow endemic zone.

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Vaccination of infants less than 9 months of age is contraindicated because of the risk of adverse reactions to yellow fever vaccination. (See CONTRAINDICATIONS section.)

**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®ACY-W135, 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, the presence of complement-fixing antibody responses to yellow fever vaccine among persons receiving chloroquine. (14) (27)

**Patients with Asymptomatic Human Immunodeficiency Virus (HIV) Infection**

The rate of seroconversion following YF-VAX is reduced in individuals with asymptomatic HIV infection and appears to depend on HIV viral load and CD4 + T-cell count. (14)

Therefore, documentation of a protective antibody response is recommended before travel. (See IMMUNE SYSTEM DISORDERS section.) For discussion of this subject and for documentation of the immune response to vaccine where it is deemed essential, contact the CDC at 1-970-221-6400.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

YF-VAX has not been evaluated for its carcinogenic or mutagenic potential or its effect on fertility.

**Pregnancy**

Animal reproduction studies have not been conducted with YF-VAX. It is also not known whether YF-VAX can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. YF-VAX should be given to a pregnant woman only if clearly needed.

YF-VAX has not been evaluated in pregnant women. However, based on experience of other yellow fever vaccines, the following findings have been determined for safety and effectiveness. Pregnant women have been vaccinated without finding that placental transfer that potentially decreases immunogenicity and increases the risk of adverse events. Intra-arterial, bursal, or tendon injections with corticosteroids should not constitute an increased hazard to recipients of yellow fever vaccine.

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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 1990 and 1991, the rate of systemic adverse events following yellow fever 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 1-800-822-7967 or https://vaers.hhs.gov.

**STORAGE**
Store at 2° to 8°C (35°F to 46°F). DO NOT FREEZE.
Do not use vaccine after expiration date. YF-VAX does not contain a preservative.

The following stability information for YF-VAX is provided for those countries or areas of the world where an adequate cold chain is a problem and inadvertent exposure to abnormal temperatures has occurred.

**YF-VAX (Yellow Fever Vaccine)** in the US is supplied only to designated Yellow Fever Vaccination Centers authorized to issue certificates of Yellow Fever Vaccination. Location of the nearest Yellow Fever Vaccination Centers may be obtained from the Centers for Disease Control and Prevention, Atlanta, GA 30333, state or local health departments.

**REFERENCES**
5. Dukes C, et al. Safety and Immunogenicity of Simultaneous Administration of Typhim Vi (TV), YF-VAX (YV), and Menomune (MV), [abstract]. American Society for Microbiology, The 36th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 1996; September 15-18.

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Product Information as of August 2019.

Manufactured by:

Sanofi Pasteur Inc.
Swiftwater, PA 18370 USA
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