PRODUCT MONOGRAPH

YF-VAX®

Yellow Fever Vaccine

(For active immunization against Yellow Fever)

ATCC: J07BL01

Sanofi Pasteur Limited
Toronto, Ontario, Canada

Date of Approval:
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YF-VAX®

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration

Subcutaneous injection

Dosage Form/Strength

Lyophilized powder for reconstitution with 0.9% Sodium Chloride diluent (provided).

Active Ingredients

Yellow fever virus strain 17D-204

Clinically Relevant Non-medicinal Ingredients

Excipients: Sorbitol, gelatin, sodium chloride injection USP

For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING.

DESCRIPTION

YF-VAX® [Yellow Fever Vaccine] is a live attenuated freeze-dried vaccine prepared by culturing the 17D-204 strain of yellow fever virus in living avian leukosis virus-free (ALV) chicken embryos. The vaccine, which contains sorbitol and gelatin as stabilizers, is lyophilized and hermetically sealed under nitrogen. No preservative is added. The vaccine must be reconstituted immediately before use with the sterile diluent provided (Sodium Chloride Injection USP - contains no preservative). After reconstitution, YF-VAX® is a slight pink-brown suspension.

YF-VAX® complies with the yellow fever vaccine standards of the World Health Organization (WHO).

INDICATIONS AND CLINICAL USE

YF-VAX® is indicated for active immunization for the prevention of yellow fever in persons 9 months of age or older. It is indicated for both primary and booster vaccination.

Yellow fever vaccination is advised for travellers passing through or living in countries in Africa, Central America and South America where yellow fever infection is officially reported. It is also recommended for travel outside of urban areas of countries that do not officially report yellow fever but lie in the yellow fever "endemic zones". (1)

Yellow fever vaccination is required by law upon entry to certain countries irrespective of the traveller's country of origin and in other countries when travellers are coming from endemic areas. In some cases, vaccination against yellow fever is recommended, although not required by

law, e.g., if yellow fever has been reported in the country of destination. In some Asian and other tropical countries where yellow fever does not exist but the transmitting mosquito is found, vaccination is required for arrivals from an endemic country to prevent importation of the disease. Current information on the countries for which an International Certificate of Vaccination or Prophylaxis is required can be obtained from local health departments or from the Public Health Agency of Canada's (PHAC) Travel Medicine Program web site. (1)

In order to comply with vaccine regulations and to be officially recognized, only designated Yellow Fever Vaccination Centre clinics approved by the PHAC and registered with the World Health Organization (WHO) may carry out yellow fever immunization, which is then recorded on an appropriately validated International Certificate of Vaccination or Prophylaxis. The period of validity of the certificate is 10 years, beginning 10 days after the date of vaccination or, in the case of a revaccination within 10 years, from the date of that revaccination. (1) (2)

Laboratory Personnel: Laboratory personnel who might be exposed to virulent yellow fever virus or to concentrated preparations of the 17D vaccine strain by direct or indirect contact or by aerosols also should be vaccinated. (3)

Geriatrics

YF-VAX® is indicated in persons 60 years of age and above. (See WARNINGS AND PRECAUTIONS, Geriatrics.)

Pediatrics

YF-VAX® is indicated in persons 9 months of age or older. (See WARNINGS AND PRECAUTIONS, Pediatrics.)

Pregnant Women

Pregnant women should be considered for immunization only if travel to an area with risk of yellow fever is unavoidable. (4) (See WARNINGS AND PRECAUTIONS, Pregnant Women.)

CONTRAINDICATIONS

Hypersensitivity

Known systemic hypersensitivity reaction to any component of YF-VAX® including latex (natural rubber) present in the vial stopper or to egg proteins, or a life-threatening reaction after previous administration of the vaccine or a vaccine containing one or more of the same components are contraindications to vaccination. (1) (5) (See SUMMARY PRODUCT INFORMATION.) Such persons may be referred to an allergist for evaluation if further immunizations are considered.

Because yellow fever virus is propagated in chick embryos, it should not be administered to persons with hypersensitivity to the ingestion of eggs or chicken protein; manifested as hives, swelling of the mouth and throat, difficult breathing, hypotension and shock. Generally, persons who are able to eat eggs or egg products may receive the vaccine. (3) If vaccination of a person with a questionable history of egg hypersensitivity is considered essential because of a high risk of exposure, an intradermal test dose may be administered under close medical supervision. (1)

Altered Immune Status

Infection with yellow fever vaccine virus poses a theoretical risk of encephalitis (see ADVERSE REACTIONS) to persons with congenital or acquired immune deficiency impairing cellular immunity including:

- Immunosuppressive therapies (e.g., high-dose corticosteroids, alkylating drugs, antimetabolites or radiation)
- Immunosuppression in association with Acquired Immunodeficiency Syndrome (AIDS) or other manifestations of Human Immunodeficiency Virus (HIV) infection, leukemia, lymphoma, thymic disease, generalized malignancy. (6)

Such persons should not be vaccinated. If travel to a yellow fever-infected zone is necessary, these persons should be advised of the risk, instructed in methods for avoiding vector mosquitoes and supplied with vaccination waiver letters by their physicians. (3)

Other

There is evidence suggesting that thymic dysfunction is an independent risk factor for the development of yellow fever vaccine-associated viscerotropic disease (7) and NACI advises health-care providers to ask about a history of thymus disorder, including myasthenia gravis, thymoma or prior thymectomy, before administering YF-VAX®. Alternative means of prevention in such persons should be considered. (1)

Infants <9 months of age

Vaccination of infants <9 months of age is contraindicated because of the increased risk of encephalitis. (8)

Nursing Women

See WARNINGS AND PRECAUTIONS, Nursing Women.

WARNINGS AND PRECAUTIONS

General

Before administration of YF-VAX®, health-care providers should inform the recipient the parent or guardian of the recipient of the benefits and risks of immunization, inquire about the recent health status of the recipient, review the recipient's history concerning possible hypersensitivity to the vaccine or similar vaccine, previous immunization history, the presence of any contraindications to immunization and comply with any local requirements regarding information to be provided to the recipient/guardian before immunization.

In analysing the risks and benefits associated with vaccination with YF-VAX®, it is important to evaluate whether the person to be vaccinated has a risk of exposure to yellow fever virus through plans for travel to a yellow fever endemic or epidemic country or area. It is also important to evaluate whether the person may have predisposing risk factors for the development of yellow fever vaccine-associated adverse events.

As with any vaccine, YF-VAX® may not protect 100% of vaccinated persons.

Administration Route Related Precautions: Do not administer YF-VAX® by intravascular injection; ensure that the needle does not penetrate a blood vessel.

Intramuscular or intradermal routes of administration are not to be utilized.

Febrile and Acute Disease: Vaccination should be postponed in cases of an acute or febrile disease. (5)

Yellow Fever Vaccine-Associated Viscerotropic Disease (YFV-AVD): Isolated cases of YFV-AVD have been reported to occur within 10 days of vaccination. (1) (3) Available evidence suggests that the occurrence of this syndrome may depend upon the presence of undefined host factors, rather than intrinsic virulence of the yellow fever strain 17D vaccine viruses isolated from subjects with vaccine-associated viscerotropic disease. (9) (10) (11) (12) The risk appears to be higher in those aged 60 years and older although cases have been reported for younger vaccinees. (13) (14) (15) (16) (See ADVERSE REACTIONS for description and further information on YFV-AVD.)

Immune

The possibility of allergic reactions in persons sensitive to components of the vaccine should be evaluated. Hypersensitivity reactions may occur following the use of YF-VAX® even in persons with no prior history of hypersensitivity to the product components.

As with all other products, epinephrine hydrochloride solution (1:1,000) and other appropriate agents should be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs. (1) Health-care providers should be familiar with current recommendations for the initial management of anaphylaxis in non-hospital settings, including proper airway management. (1) For instructions on recognition and treatment of anaphylactic reactions, see the current edition of the Canadian Immunization Guide or visit the Health Canada website.

The stopper of the vial for this product contains latex (natural rubber). Latex has been associated with allergic reactions.

Since the yellow fever virus is propagated in chicken embryos, it should not be administered to any person with a history of hypersensitivity to egg or chicken protein. (See CONTRAINDICATIONS.) In some instances, although symptoms appear soon after a vaccine is administered, differentiation between allergic reaction to the vaccine and reaction to an environmental allergen is impossible. (17)

Less severe or localized manifestations of allergy to egg or to feathers are not contraindications to vaccine administration and do not usually warrant vaccine skin testing. (17)

Persons with egg-sensitivity should be referred to an allergist as vaccination might be possible after careful evaluation, skin-testing and graded challenge or desensitization. (1)

Altered Immune Status: YF-VAX® should not routinely be administered to immunocompromised persons. An individual risk assessment should be carried out, weighing the true risk of disease and the degree to which the patient is immunocompromised. (1) (See CONTRAINDICATIONS.) In instances where immunocompromised persons are vaccinated, the seroconversion rate after administration of yellow fever vaccine may be significantly reduced. (18) (19)

Asymptomatic HIV-infected persons, who have laboratory-verified adequate immune system function and who cannot avoid potential exposure to yellow fever virus should be offered the choice of vaccination. Vaccinees should be monitored for possible adverse effects. The vaccination of such persons may be less effective than that for non-HIV-infected persons. Family members of immunosuppressed persons, who themselves have no contraindication, may receive yellow fever vaccine. (3)

Neurologic

Yellow Fever Vaccine-Associated Neurotropic Disease (YFV-AND): Isolated cases of YFV-AND (see ADVERSE REACTIONS) have been reported to occur within a month of vaccination. Known risk factors for this adverse event are age <9 months and congenital or acquired immunodeficiency. (8) (See CONTRAINDICATIONS and ADVERSE REACTIONS.)

Pregnant Women

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 reproductive capacity. Because of the lack of large-scale, controlled studies to verify its safety in pregnancy, YF-VAX® should be given to a pregnant woman only if the benefit of preventing the disease is deemed to outweigh the potential risk from the vaccine.

If international travel requirements are the only reason to vaccinate a pregnant woman, rather than an increased risk for infection, efforts should be made to obtain a waiver letter from the traveller's physician. (3)

Although the seroconversion rate after yellow fever vaccination during pregnancy may be significantly reduced, (18) pregnant women who must travel to areas where the risk for yellow fever infection is high should be vaccinated and despite the apparent safety of this vaccine, infants born to these women should be monitored closely for evidence of congenital infection and other possible adverse effects resulting from yellow fever vaccination. (3) Information from limited clinical trials in Africa and Europe indicated that the risk from vaccination for pregnant women who cannot avoid mosquito exposure in yellow-fever endemic areas is outweighed by the risk for yellow fever infection. (3)

Nursing Women

It is not known whether this vaccine is excreted in human milk. However, breast-feeding infant Yellow Fever encephalitis has been very rarely reported following maternal vaccination with live attenuated yellow-fever vaccine. The vaccination of nursing women should be avoided when possible, particularly when infants are under 9 months of age, (8) because of the probable risk of the transmission of 17D virus to the breast-fed infant (See WARNINGS AND PRECAUTIONS, Pediatrics). When travel of nursing women to high-risk yellow fever endemic areas cannot be avoided or postponed, such individuals may be immunized. (3)

Pediatrics

YF-VAX® is contraindicated in infants <9 months of age because of the risk of encephalitis (see ADVERSE REACTIONS) and travel of such persons to rural areas in yellow fever endemic

zones or to countries experiencing an epidemic should be postponed or avoided, whenever possible.

Geriatrics

Analysis of adverse events reported after administration of yellow fever vaccines demonstrated an increased frequency of serious adverse events (neurologic or systemic reactions persisting more than 48 hours) including yellow fever vaccine-associated viscerotropic disease, in persons 60 years of age and older when compared to other age groups. Therefore, vaccination of persons older than 60 years of age should be limited to persons who are travelling to or reside in known yellow fever endemic or epidemic areas. When vaccination of persons over the age of 60 is deemed necessary, an individual risk assessment should be made before vaccination, including an evaluation of the health status of these persons. (13) (14) (15) (16) Additionally, elderly persons who are vaccinated should be carefully monitored for adverse events for 10 days post-vaccination. (13) (See ADVERSE REACTIONS.)

ADVERSE REACTIONS

Adverse Reaction Overview

Adverse reactions to 17D yellow fever vaccines are generally mild. Two to 5% of vaccinees report mild headaches, myalgia, low-grade fevers or other minor symptoms for 5 to 10 days after vaccination. Fewer than 0.2% of the vaccinees curtail regular activities. (1) (3) (20) (21) In clinical studies, the most common adverse events occurring after vaccine administration were injection site reactions. (22) (23) Injection site reactions including edema, hypersensitivity, pain or mass at the injection site have been reported following yellow fever vaccine administration. (20)

Clinical Trial Adverse Reactions

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to vaccine use and for approximating rates of those events.

In 2001, YF-VAX® was used as a control in a double-blind, randomized comparative trial with another 17D-204 vaccine, conducted at nine centres in the US. YF-VAX® was administered to 725 adults 18 years-old and above, with a mean age of 38 years. (22) There were no serious adverse events and 71.9% of the participants who received YF-VAX® experienced one or more non-serious vaccine-related adverse event. Most of these were injection site reactions of mild to moderate severity.

Nervous System Disorders

Very Common ≥10%	Headache

Gastrointestinal System Disorders

Common ≥1% and <10%	Nausea

Immune System Disorders

Common ≥1% and <10%	Hypersensitivity reactions such as rash and urticaria

Musculoskeletal and Connective Tissue Disorders

Very Common ≥10%	Myalgia

General Disorders and Administration Site Conditions

Very Common ≥10%	Injection site reactions (erythema, pain or mass)
	Pyrexia, asthenia

Data from Post-Marketing Experience

The following additional adverse events have been spontaneously reported during the post-marketing use of YF-VAX® worldwide. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Decisions to include these events in labelling were based on one or more of the following factors: 1) severity of the event, 2) frequency of reporting, or 3) strength of causal connection to YF-VAX®.

Immune System Disorders (8)

Immediate hypersensitivity reactions, characterized by rash and/or urticaria

Nervous System Disorders (21) (24) (25) (26)

Isolated cases of Neurotropic disease, described as Yellow Fever Vaccine-Associated Neurotropic Disease (YFV-AND), sometimes fatal, have been reported to occur within 30 days following vaccination with YF-VAX® and also with other Yellow Fever vaccines. The clinical presentation has varied and includes high fever with headache associated with one or more of confusion, lethargy, encephalitis, encephalopathy and meningitis. Age <9 months and congenital or acquired immunodeficiency have been identified as risk factors for this event.

Other neurological signs and symptoms have been reported and include Guillain-Barré syndrome (27), seizures and focal neurological deficits. (28)

General Disorders and Administration Site Conditions

Isolated cases of Yellow Fever Vaccine-Associated Viscerotropic Disease (8) (YFV-AVD formerly described as "Febrile Multiple Organ-System-Failure"), sometimes fatal, have been reported following YF-VAX® and also following administration of yellow fever vaccines from other manufacturers. In the majority of cases reported, the onset of signs and symptoms was within 10 days after the vaccination. Initial signs and symptoms are non-specific and may include pyrexia, myalgia, fatigue and headache, potentially progressing quickly to liver and muscle cytolysis and possibly to thrombocytopenia, lymphopenia and acute renal failure. (9) The pathophysiological mechanism of such reactions has not been established. In some individuals with yellow fever vaccine-associated viscerotropic disease a medical history of thymic disease has been reported. (29) Age greater than 60 has also been identified as a risk factor for this event. (30)

Physicians, nurses and pharmacists should report any adverse occurrences temporally related to the administration of the product in accordance with local requirements and to the Global Pharmacovigilance Department, Sanofi Pasteur Limited, 1755 Steeles Avenue West, Toronto, ON, M2R 3T4, Canada. 1-888-621-1146 (phone) or 416-667-2435 (fax).

DRUG INTERACTIONS

Vaccine-Drug Interactions

Immunosuppressive treatments may be a contraindication to the administration of YF-VAX® due to the increased risk of severe adverse reactions linked to immunodepression. (See CONTRAINDICATIONS, Altered Immune Status.) Immunosuppressive treatments may also interfere with the development of the expected immune response. (See WARNINGS AND PRECAUTIONS.)

YF-VAX® can be administered with the anti-malarial drug chloroquine. (8) (31)

Concomitant Vaccine Administration

There are obvious practical advantages to giving more than one vaccine at the same time, especially in preparation for foreign travel or when there is doubt that the patient will return for further doses of vaccine.

Data are limited in regard to the interaction of YF-VAX® with other vaccines. Studies have shown that the serologic response to yellow fever vaccine is not inhibited by the administration of certain other vaccines concurrently at separate sites or at various intervals of a few days to one month. (32) Measles (Schwartz strain) vaccine, smallpox, diphtheria and tetanus toxoids and pertussis vaccine adsorbed (DTP), (33) hepatitis A vaccine, (34) (35) hepatitis B vaccine, (36) meningococcal vaccine, MENOMUNE® A/C/Y/-W-135 and typhoid vaccine, TYPHIM Vi® (34) (37) have been administered concurrently with yellow fever vaccine at separate injection sites.

No data exists on possible interference between yellow fever and rabies or Japanese encephalitis vaccine.

Concurrent administration of other live vaccines, including live oral cholera, live oral typhoid vaccines or with DUKORAL® (Oral, Inactivated Travellers' Diarrhea and Cholera Vaccine), (20) does not inhibit the serological response to yellow fever vaccine.

If live vaccines are not given concurrently, they should be spaced at least 4 weeks apart. (1) Inactivated vaccines (except inactivated parenteral cholera vaccine) may also be administered during the same patient visit with other vaccines commonly administered to international travelers or at any interval after. (1)

The administration of immune globulin and yellow fever vaccine either simultaneously or within a short span of time, does not alter the immunologic response. (4) (32)

Vaccines administered simultaneously should be given using separate syringes at separate sites. YF-VAX® should not be mixed in the same syringe with other parenterals.

DOSAGE AND ADMINISTRATION

Recommended Dose

Primary Vaccination: For persons of all ages, YF-VAX® should be administered by the subcutaneous route as a single injection of 1 dose (0.5 mL). (1)

Booster Dose: The International Health Regulations require revaccination at intervals of 10 years. Revaccination boosts antibody titre; however, evidence from several studies suggests that yellow fever vaccine immunity persists for at least 30 to 35 years and probably for life. (1)

Do not dilute reconstituted vaccine (except for administration following a desensitization procedure).

Administration

Inspect for extraneous particulate matter and/or discolouration before use. (See DESCRIPTION.) If these conditions exist, the product should not be administered.

Reconstitution of Freeze-Dried Product and Withdrawal from Stoppered Vial

When withdrawing from a stoppered vial, do not remove either the stopper or the metal seal holding it in place. Reconstitute the vaccine using only the supplied diluent (Sodium Chloride Injection USP). Draw the volume of the diluent shown on the diluent label into a syringe of suitable size. Slowly inject the diluent into the vial containing the vaccine, let stand for one or two minutes and then carefully swirl mixture until a uniform suspension is achieved. Avoid vigorous shaking as this tends to cause foaming of the suspension. Use vaccine within 60 minutes following reconstitution.

Withdraw the required dose (0.5 mL) of the reconstituted vaccine into a syringe. Use a separate sterile needle and syringe, or a sterile disposable unit for each individual patient to prevent disease transmission. Needles should not be recapped and should be disposed of according to biohazard waste guidelines. (See WARNINGS AND PRECAUTIONS.)

SWIRL THE PRODUCT VIAL WELL before withdrawing each dose.

Before injection, the skin over the site to be injected should be cleansed with a suitable germicide. If a germicide is used to cleanse the skin before immunization, the skin must be allowed to dry thoroughly before the vaccine is administered to prevent inactivation of the vaccine by the germicide.

Administer the total volume of 0.5 mL **subcutaneously**.

Give the patient a permanent personal immunization record. In addition, it is essential that the physician or nurse record the immunization history in the permanent medical record of each patient. This permanent office record should contain the name of the vaccine, date given, dose, manufacturer and lot number.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Yellow fever is an acute viral illness caused by a mosquito-borne flavivirus. Infection with the virus may cause a potentially lethal pansystemic disease with fever, jaundice, renal failure and hemorrhage. (21) YF-VAX® is a live, attenuated yellow fever vaccine made from the 17D-204 virus strain. Vaccination with 17D strain viruses is predicted to elicit an immune response identical in quality to that induced by wild-type infection. This response is presumed to result from initial infection of cells in the dermis or other subcutaneous tissues near the injection site, with subsequent replication and limited spread of virus. This leads to the processing and presentation of viral antigens to the immune system, as would occur during infection with wild-type yellow fever virus.

Pharmacodynamics

Immunity develops 10 days after vaccination. (21) (41)

The neutralizing antibody response to 17D vaccines has been evaluated in several studies since the late 1930s. In studies conducted worldwide since 1962, using 17D vaccines in 2,529 adults and 991 infants and children, the seroconversion rates were between 91% and 100% in all but two studies and never lower than 81%. There were no significant age-related differences in immunogenicity. (21) (22)

Duration of Effect

Immunity elicited by yellow fever vaccination persists for more than 10 years. (1) (38)

STORAGE AND STABILITY

Store at 2° to 8°C (35° to 46°F). **Do not freeze.**

The vial of diluent should not be allowed to freeze. Do not use vaccine after expiration date.

The reconstituted vaccine must be kept refrigerated and used within 60 minutes following reconstitution.

SPECIAL HANDLING INSTRUCTIONS

All reconstituted vaccine and containers which remain unused after one hour must be disposed of properly (e.g., sterilized or disposed in hazardous waste containers)**.**

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

YF-VAX® is supplied as a sterile lyophilized powder in either 1 dose or 5 dose vial.
The diluent (Sodium Chloride Injection USP - contains no preservative) is supplied in 3 mL or 0.6 mL Vials.
After reconstitution, YF-VAX® is a slight pink-brown suspension.

Composition

YF-VAX® is a live attenuated freeze-dried vaccine prepared by culturing the 17D-204 strain of yellow fever virus in living avian leukosis virus-free (ALV) chicken embryos. The vaccine, which contains sorbitol and gelatin as stabilizers, is lyophilized and hermetically sealed under nitrogen. No preservative is added. The vaccine must be reconstituted immediately before use with the sterile diluent provided (Sodium Chloride Injection USP - contains no preservative).

Each single dose (0.5 mL) is formulated to contain:

Active Ingredients

Yellow Fever Virus strain 17D-204	≥4.74 $\log_{10}$	Plaque Forming Units (PFU) throughout the life of the product

Other Ingredients

Excipients:	
Sorbitol	<7.5 mg
Gelatin	<7.5 mg
Diluent:	
Sodium Chloride Injection USP	0.9%

Packaging

YF-VAX® is supplied in single and five dose vials with accompanying diluent. The vials are made of Type 1 glass.

The vaccine stoppers do not contain latex (natural rubber). The diluent stoppers contain latex (natural rubber).

YF-VAX is available in a package of:

1 x 5 dose vial of vaccine and package of 1 x 3 mL vial of diluent.

5 x 1 dose vials of vaccine and package of 5 x 0.6 mL vials of diluent.

Vaccine Information Service: 1-888-621-1146 or 416-667-2779. Business hours: 8 a.m. to 5 p.m. Eastern Time, Monday to Friday.

Full product monograph available on request or visit us at www.sanofipasteur.ca

Product information as of December 2009.

Manufactured by:
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Swiftwater, PA 18370 USA

Distributed by:
Sanofi Pasteur Limited
Toronto, Ontario, Canada

R15-1209 Canada

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Yellow Fever Vaccine

Product Characteristics

YF-VAX® is a live attenuated freeze-dried vaccine prepared by culturing the 17D-204 strain of yellow fever virus in living avian leukosis virus-free (ALV) chicken embryos. The vaccine, which contains sorbitol and gelatin as stabilizers, is lyophilized and hermetically sealed under nitrogen. No preservative is added. The vaccine must be reconstituted immediately before use with the sterile diluent provided (Sodium Injection USP - contains no preservative). YF-VAX® is formulated to contain not less than 4.74 $\log_{10}$ PFU per 0.5 mL dose throughout the life of the product. After reconstitution, YF-VAX® is a slight pink-brown suspension.

YF-VAX® complies with the standards of the World Health Organization (WHO).

CLINICAL TRIALS

Immunogenicity

The neutralizing antibody response to 17D vaccines has been evaluated in several controlled and non-controlled studies since the late 1930s. In studies conducted worldwide since 1962, using 17D vaccines in 2,529 adults and 991 infants and children, the seroconversion rates were between 91% and 100% in all but two studies and never lower than 81%. There were no significant age-related differences in immunogenicity. (21) (22)

In 2001, YF-VAX® was used as a control in a double-blind, randomized comparative trial with another 17D-204 vaccine, conducted at nine centres in the US. YF-VAX® was administered to 725 adults ≥18 years old with a mean age of 38 years. Three hundred twelve subjects who received YF-VAX® were evaluated serologically. A log neutralization index (LNI) of 0.7 or higher was considered evidence of seroconversion. A month after immunization, 99.3% of subjects receiving YF-VAX® had 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 these differences were not significant with respect to the protective effect of the vaccine. There was no difference in mean LNI for subjects <40 years old compared to subjects ≥40 years old.

Results of one clinical trial involving 33 HIV-positive American adults indicate that the seroconversion rate to 17D-204 vaccine may be reduced in these patients. (19)

Safety

Among participants in the 2001, double-blind, randomized comparative trial who received YF-VAX®, there were no serious adverse events and 71.9% experienced non-serious adverse events judged to have been related to vaccination. Most of these were injection site adverse events of

mild to moderate severity. Four of these injection site adverse events were considered severe. Systemic reactions were usually mild and occurred in 1.4 to 31.4% of subjects during the first few days after vaccination. Rash occurred in 3.2% of participants and urticaria was observed in two participants (0.3%). The incidence of non-serious adverse reactions, including headache, malaise, injection site edema and pain, was significantly lower in subjects >60 years compared to younger subjects. Adverse events were less frequent in the 1.7% of vaccinated subjects who had pre-existing immunity to yellow fever virus, compared to those who had not been previously exposed. (22)

In this clinical trial, injection site pain was reported in 39.4%, injection site inflammation in 29.4%, injection site edema in 19.9% and an injection site reaction in 5.7%, following administration of YF-VAX®. (22)

Pregnancy

In a study involving 101 Nigerian women in various stages of pregnancy, it was concluded that vaccinating pregnant women with the 17D strain of yellow fever vaccine was not associated with adverse effects on the fetus or with risk of fetal infection. However, the percentage of pregnant women without neutralizing antibodies, who seroconverted, was significantly less than a non-pregnant control group (38.6% vs. 81.5%). (18) On the basis of clinical evaluation of 81 infants in two different studies who were born to mothers vaccinated in pregnancy, infection of the fetus with 17D strains of yellow fever vaccine occurs at a low rate (i.e., 1 of 81) and has not been associated with congenital abnormalities. (3) (18) (39) In a recent case-controlled study of women inadvertently vaccinated with a 17D yellow fever vaccine early in pregnancy, no statistically significant increase in rates of spontaneous abortion were observed. (3) (40) Information from limited clinical trials in Africa and Europe indicated that the risk from vaccination for pregnant women who cannot avoid mosquito exposure in yellow-fever endemic areas is outweighed by the risk for yellow fever infection. (3)

DETAILED PHARMACOLOGY

Yellow fever (YF) is a zoonotic hemorrhagic fever caused by a flavivirus transmitted by *Aedes aegypti* mosquitoes. YF evolves through a spectrum of three periods of illness, from a non-specific febrile illness with headache, malaise, weakness, nausea and vomiting, through a brief period of remission, to a hemorrhagic fever with gastrointestinal tract bleeding and hematemesis, jaundice, hemorrhage, cardiovascular instability, albuminuria, oliguria and myocarditis. There is a 20% to 30% case fatality rate.

YF is endemic in the tropical areas of equatorial sub-Saharan Africa, Panama in Central America and the tropical region of South America. It does not occur in Asia, although the vector *Aedes aegypti* is present there.

Worldwide, 90% of YF cases occur in Africa and 10% in the Americas. The disease manifests itself in two epidemiologic forms, the urban and the sylvatic or jungle, both forms caused by the same virus. Urban disease is a particular problem in Africa and a potential problem in South America. Jungle YF is a disease transmitted by tree-hole breeding mosquitoes to monkeys in the forests of South America and Africa and can be transmitted to humans.

Disease control includes protection from *Aedes* mosquitoes, which are primarily day-biting, elimination of *A. aegypti* from urban areas and immunization of those at risk of exposure. Unimmunized Canadians can acquire YF when travelling abroad but cannot transmit the disease on their return to Canada, since the recognized mosquito vectors are not present in this country.

Since 1996 there have been reports of YF occurring in American and European travellers visiting YF endemic areas of Africa and South America. Notably, none of these tourists had received YF vaccine. (41) There have been no cases of YF reported to PHAC since surveillance began in 1924.

YF-VAX® is a live, attenuated yellow fever vaccine made from the 17D-204 virus strain. Vaccination with 17D strain viruses is predicted to elicit an immune response identical in quality to that induced by wild-type infection. This response is presumed to result from initial infection of cells in the dermis or other subcutaneous tissues near the injection site, with subsequent replication and limited spread of virus. This leads to the processing and presentation of viral antigens to the immune system, as would occur during infection with wild-type yellow fever virus. Immunity develops 10 days after vaccination and persists for more than 10 years. (21) (41)

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Vaccine Information Service: 1-888-621-1146 or 416-667-2779. Business hours: 8 a.m. to 5 p.m. Eastern Time, Monday to Friday.

Full product monograph available on request or visit us at www.sanofipasteur.ca

Product information as of December 2009.

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Sanofi Pasteur Inc.
Swiftwater, PA 18370 USA

Distributed by:
Sanofi Pasteur Limited
Toronto, Ontario, Canada

R15-1209 Canada

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

YF-VAX®
Yellow Fever Vaccine

This leaflet is part III of a three-part "Product Monograph" published when YF-VAX® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about YF-VAX®. Contact your doctor or nurse if you have any questions about the vaccine.

ABOUT THIS VACCINE

What the vaccine is used for:

YF-VAX® is a vaccine that is used to help prevent yellow fever. This vaccine may be given to adults and children 9 months of age and older who are:

- travelling to or living in countries and areas where yellow fever infection is officially reported or considered to exist.
- travelling to countries where yellow fever vaccination is required by law upon entry. Current information on the countries for which an International Certificate of Vaccination or Prophylaxis is required can be obtained from local public health departments or from the Public Health Agency of Canada's (PHAC) Travel Medicine Program web site.
- laboratory personnel who might be exposed to yellow fever virus or to concentrated preparations of the 17D vaccine strain.

The majority of persons who are vaccinated with YF-VAX® will produce enough antibodies to protect them from this disease. However, as with all vaccines, 100% protection cannot be guaranteed.

What the vaccine does:

YF-VAX® causes your body to produce its own natural protection against the yellow fever virus. After you receive the vaccine, your body begins to make substances called antibodies. Antibodies help your body to fight disease. If a vaccinated person comes into contact with the yellow fever virus, the body is usually ready to destroy it.

When the vaccine should not be used:

Do not give YF-VAX® to:

- persons who are known to have a severe allergy to any ingredient in the vaccine, including latex in the container, eggs and chicken protein, or who have had a severe allergic reaction after receiving a vaccine that contained similar ingredients.
- persons who have a weakened immune system because of cancer, HIV/AIDS or another disease that affects the immune system; treatment with drugs that affect the immune system such as steroids, cancer treatment with drugs or radiation.
- persons whose thymus gland has been removed, or have a history of problems with the thymus such as myasthenia gravis or thymoma.

What the medicinal ingredient is:

Each 0.5 mL dose of YF-VAX® contains: 17D-204 strain of yellow fever vaccine virus which has been grown in chicken eggs.

What the important non-medicinal ingredients are:

Vaccine: Sorbitol, gelatin
Diluent: Sodium Chloride

What dosage forms it comes in:

YF-VAX® is a powder and diluent for suspension that is mixed and injected subcutaneously (just under skin). A single dose is 0.5 mL.

WARNINGS AND PRECAUTIONS

If you or your child has any of the following conditions, talk to your doctor or nurse BEFORE you or your child receives YF-VAX®:

- **A high fever or serious illness**. Delay the vaccination until the person is better.
- **An allergy to any component of the vaccine, eggs, chicken protein, or the latex in the container.**
- **Pregnant or nursing women.** It is important that you understand the risks and benefits of vaccination. YF-VAX® should be given to a pregnant or nursing woman only if it is clearly needed. Tell the person giving you the injection if you are pregnant or breast-feeding.

Age-related precautions:

- **Age 60 years and above.** Discuss with your doctor or nurse the risks and benefits of vaccination in the context of your risk for exposure to yellow fever virus at your destination.

INTERACTIONS WITH THIS VACCINE

DO NOT mix YF-VAX® with other vaccines or medicinal products in the same syringe.

PROPER USE OF THIS VACCINE

Usual Dose:

For persons 9 months of age and older - single dose of 0.5 mL.

The vaccination should be given subcutaneously (just under the skin).

Booster doses: People who continue to live in or travel to yellow-fever endemic areas should receive a booster dose of YF-VAX® after 10 years.

Yellow fever vaccine is only given at approved vaccination centres. After receiving vaccine, you should receive an International Certificate of Vaccination or Prophylaxis that has been validated by the vaccination centre.

Overdose: Not applicable to this vaccine.

Missed Dose: Not applicable to this vaccine.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

A vaccine, like any medicine, may cause serious problems, such as severe allergic reactions. The risk of YF-VAX® causing serious harm is extremely small. The small risks associated with YF-VAX® are much less than the risks of getting the disease associated with situations listed under 'About this Vaccine'.

Tell your doctor or nurse as soon as possible if you do not feel well after receiving YF-VAX®.

Some people who receive YF-VAX® may have mild side effects such as soreness, redness or swelling at the site of the injection. The side effects usually go away within a few days.

Life-threatening severe illness with multiple organ failure has been reported very rarely. It is reported that adults aged 60 years and over are at higher risk compared with other age groups.

Severe nervous system reactions have been reported very rarely. It is reported that adults aged 60 years and over and young infants are at higher risk compared with other age groups.

This is not a complete list of side effects. For any unexpected effects while taking YF-VAX®, contact your doctor or nurse.

HOW TO STORE IT

Store the vaccine in a refrigerator at 2° to 8°C (35° to 46°F). **Do not freeze.**

After mixing, YF-VAX® must be stored in a refrigerator and used within 60 minutes.

Do not use vaccine after expiration date.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects information on serious and unexpected adverse events following vaccination.

If you suspect you have had a serious or unexpected event following receipt of a vaccine you may notify the Public Health Agency of Canada:

toll-free telephone: 613-954-5590 (1-866-844-0018)

toll-free fax: 613-954-9874 (1-866-844-5931)

email: caefi@phac-aspc.gc.ca

regular mail:
Vaccine Safety Section
Centre for Immunization & Respiratory Infectious Diseases
Public Health Agency of Canada
130 Colonnade Road, A/L 6502A
Ottawa, Ontario
K1A 0K9

Note: Should you require information related to the management of the side effect, please contact your health care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at www.sanofipasteur.ca

You may also contact the vaccine producer, Sanofi Pasteur Limited, for more information. Telephone 1-888-621-1146 (no charge) or 416-667-2779 (Toronto area). Business hours: 8 a.m. to 5 p.m. Eastern Time Monday to Friday.

This leaflet was prepared by Sanofi Pasteur Limited.

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