PRODUCT MONOGRAPH

AVAXIM®

Hepatitis A Vaccine Inactivated

Dosage Form: Single Dose Syringe

Active Immunizing Agent
(For the Prevention of Hepatitis A Infection)

Manufactured by:
Sanofi Pasteur SA
Lyon, France

Distributed by:
Sanofi Pasteur Limited
Toronto, Ontario, Canada

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CLINICAL PHARMACOLOGY

Hepatitis A results from infection of the liver by hepatitis A virus (HAV), an RNA virus of a single serotype. Infection usually causes overt illness in adults and school-age children but is often asymptomatic in younger children. Humans are the principal reservoir for the virus. Typical symptoms of illness include anorexia, nausea, fatigue, fever and jaundice. Recovery often takes 4 to 6 weeks. About 25% of reported adult cases require hospitalization. Fulminant disease with liver necrosis is rare but can be fatal. The estimated mortality rate associated with hepatitis A is 0.1 - 0.3%, but this rises to 1.8% in persons over the age of 50.[1] Individuals with pre-existing chronic liver disease are at increased risk of serious complications from hepatitis A infection.[1]

Risk factors for infection in Canada include the following:[1]

- residence in certain communities in rural or remote areas lacking adequate sanitation;
- residence in certain institutions, such as correctional facilities and those for developmentally challenged persons;
- oral or intravenous illicit drug use;
- sexual behaviours involving anal contact, particularly between men;
- travel to or residence in countries with inadequate sanitation.

Hepatitis A virus (HAV) infection in returned travellers and contacts of travellers including children account for a large proportion of cases reported in Canada; some cases have occurred in people who spent <2 weeks in an endemic area.[1] The risk for susceptible travellers to developing countries has been estimated at 3 to 5 per 1,000 per month and is up to six times higher for low-budget travellers eating in poorer hygienic conditions.[2] In Canada, between 1990 and 1999, the annual number of cases of HAV infection reported to the National Notifiable Disease Registry varied from 890 to 3,020, with corresponding rates from 3.0 to 10.8 per 100,000 population. Given under-reporting and asymptomatic infection, however, the actual number of cases is considerably higher. In 1999, the reported rate was 1.6 times higher among males than females. Age-specific incidence rates were highest among those 25 to 59 years of age and lowest among those <5 years or >59 years; 18% of all cases were <15 years old, an age group in which the

disease is often asymptomatic. Although representative data are not available for the general Canadian population, studies indicate that immunity to HAV infection is evident in about 3% of Canadian-born preadolescents and in over 60% of those 60 years of age. The difference in levels of immunity reflects progressive accumulation of immunity over time and the greater likelihood of exposure in the past, when the infection was more common. Overall, the most commonly identified risk factor for HAV infection is household or sexual exposure to a recent case. In many infected persons no specific risk factor can be identified.[1]

AVAXIM® [Hepatitis A Vaccine Inactivated] confers immunity against hepatitis A virus (HAV) infection by inducing the production of specific anti-hepatitis A virus antibodies.

Clinical studies indicate that the vaccine confers immunity against hepatitis A virus by inducing antibody titres greater than those obtained after passive immunization with immunoglobulin. Immunity appears shortly after the first injection.

In clinical studies involving over 1,000 volunteers, specific humoral antibodies against hepatitis A were elicited after the first injection and more than 90% of immunocompetent subjects were protected (titres above 20 mIU/mL) 14 days after vaccination. One month after the first injection, 100% of the subjects were protected. Immunity persisted for at least six months and was reinforced after a first booster dose.

In comparative trials with another hepatitis A vaccine, AVAXIM® demonstrated a superior immunogenicity profile. Additionally, seroconversion rates at 14 days showed that the immune responses occur more rapidly with AVAXIM®.[3,4] This prompt immune response may be an important consideration when travellers must be vaccinated immediately prior to departure or when post-exposure prophylaxis cannot be done immediately after exposure.[5]

INDICATIONS AND CLINICAL USE

AVAXIM® [Hepatitis A Vaccine Inactivated] is indicated for active immunization against infection caused by hepatitis A virus (HAV) in persons 12 years of age and older. AVAXIM® can be used for primary immunization or as a booster following primary immunization with AVAXIM® or other similar hepatitis A vaccines.[5,6]

AVAXIM® is recommended for pre-exposure prophylaxis of individuals at increased risk of infection. Potential candidates for the vaccine are: [1]

- travellers to countries where hepatitis A is endemic, especially when travel involves rural or primitive conditions;
- residents of communities with high endemic rates or recurrent outbreaks of HAV;
- members of the armed forces, emergency relief workers and others likely to be posted abroad at short notice to areas with high rates of HAV infection;
- residents and staff of institutions for the developmentally challenged where there is an ongoing problem with HAV transmission;
- inmates of correctional facilities in which there is an ongoing problem with HAV infection;
- people with life-style determined risks of infection, including those engaging in oral or intravenous illicit drug use in unsanitary conditions;
- men who have sex with men;

- people with chronic liver disease who may not be at increased risk of infection but are at increased risk of fulminant hepatitis A;
- patients with hemophilia A or B receiving plasma-derived replacement clotting factors;
- zoo-keepers, veterinarians and researchers who handle non-human primates;
- certain workers involved in research on hepatitis A virus or production of hepatitis A vaccine.

Outbreak Control[1]

AVAXIM® should be used as part of a coordinated public health response to hepatitis A outbreaks. Hepatitis A Vaccine has been used to arrest the transmission of the virus in communities.

Universal Immunization[1]: WHO recommends targeted programs for countries with low endemicity, such as Canada.

CONTRAINDICATIONS

General

Immunization with AVAXIM® [Hepatitis A Vaccine Inactivated] should be deferred in the presence of any acute illness, including febrile illness to avoid superimposing adverse effects from the vaccine on the underlying illness or mistakenly identifying a manifestation of the underlying illness as a complication of vaccine use. A minor afebrile illness such as mild upper respiratory infection is not usually reason to defer immunization.[1]

Allergy to any component of AVAXIM® (see components listed in PHARMACEUTICAL INFORMATION and AVAILABILITY OF DOSAGE FORMS) or an anaphylactic or other allergic reaction to a previous dose of AVAXIM® are contraindications to vaccination.

The vaccine should not be administered intravenously or intradermally.

WARNINGS

AVAXIM® [Hepatitis A Vaccine Inactivated] does not provide protection against infection caused by hepatitis B virus, hepatitis C virus, delta virus, hepatitis E virus, or by other liver pathogens, other than hepatitis A virus.

Seropositivity against hepatitis A virus is not a contraindication. AVAXIM® is as well tolerated in seropositive as in seronegative subjects.[3]

Because of the incubation period of hepatitis A, infection may be present at the time of vaccination; if so, the vaccine may be ineffective.

Intramuscular injections should be given with care in persons suffering from coagulation disorders or on anticoagulant therapy because of the risk of hemorrhage.[1]

AVAXIM® should not be administered into the buttocks due to the varying amount of fatty tissue in this region, nor by the intradermal route, since these methods of administration may induce a weaker immune response.

Immunocompromised persons (whether from disease or treatment) may not obtain the expected immune response. If possible, consideration should be given to delaying vaccination until after the completion of any immunosuppressive treatment.[3] If AVAXIM® is used in these persons, seroconversion should be

confirmed by antibody testing.

As with any vaccine, immunization with AVAXIM® may not protect 100% of susceptible individuals.

PRECAUTIONS

The possibility of allergic reactions in persons sensitive to components of the vaccine should be evaluated. 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.[1,7]

For instructions on recognition and treatment of anaphylactic reactions see the current edition of the Canadian Immunization Guide or visit the Health Canada website.

Before administration, take all appropriate precautions to prevent adverse reactions. This includes a review of the patient's history concerning possible hypersensitivity to the vaccine or similar vaccine, previous immunization history, the presence of any contraindications to immunization and current health status and a current knowledge of the literature concerning the use of the vaccine under consideration.

Before administration of AVAXIM® [Hepatitis A Vaccine Inactivated], health-care providers should inform the parent or guardian or the patient to be immunized of the benefits and risks of immunization, inquire about the recent health status of the patient and comply with any local requirements with respect to information to be provided to the patient before immunization.

Do not inject into a blood vessel.

Use a separate sterile needle and syringe, or a sterile disposable unit, for each individual patient to prevent disease transmission.

There have been case reports of transmission of HIV and hepatitis by failure to scrupulously observe sterile technique.[8]

Pregnancy and Lactation

The effect of AVAXIM® on the development of the embryo and fetus has not been assessed. Vaccination in pregnancy is not recommended unless there is a definite risk of acquiring hepatitis A. As the vaccine is inactivated, any risk to the embryo or the fetus is improbable. The benefits versus the risks of administering AVAXIM® in pregnancy should carefully be evaluated.

The effect of administration of AVAXIM® during lactation has not been assessed. As AVAXIM® is inactivated, any risk to the mother or the infant is improbable. The benefits versus the risks of administering AVAXIM® during lactation should carefully be evaluated.

Drug Interactions

If indicated, AVAXIM® may be administered simultaneously with immune globulin at separate sites with separate syringes.[1] Seroconversion rates are not modified, but antibody titres could be lower than after vaccination with the vaccine alone.[9]

As the vaccine is inactivated, concomitant administration of other vaccine(s) given at other injection sites is unlikely to interfere with immune responses. No interaction with other medication is currently known. AVAXIM® has been shown to be safe and immunogenic when concomitantly administered with TYPHIM Vi® using separate syringes at different sites.[10]

Pediatric Use

AVAXIM® is indicated for persons 12 years of age and older. AVAXIM®-Pediatric, is used for children aged 12 months to 15 years of age. Either vaccine may be used for persons between 12 to 15 years of age.

ADVERSE REACTIONS

In six clinical trials conducted which involved over 2,200 participants, adverse events were usually mild and confined to the first few days after vaccination with spontaneous recovery. The most common local reaction was mild pain (11.7%) at the injection site, occasionally associated with redness (0.5% over 3 cm). Mild fever (5.2%), weakness (13.5%), headache (9.7%), muscle or joint ache (10.3%) or gastro-intestinal tract disorders (6.1%) such as nausea, vomiting, diarrhea, or pain, were also reported.

Mild transient elevation of serum transaminases has been reported on rare occasions.

Adverse reactions were less frequently reported after the booster dose than after the first dose. In subjects seropositive to HAV, AVAXIM® [Hepatitis A Vaccine Inactivated], was as well tolerated as in seronegative subjects.

In comparative trials with another hepatitis A vaccine, in a total of 423 adults, AVAXIM® demonstrated significantly fewer local reactions after each injection.[3]

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).

DOSAGE AND ADMINISTRATION

Primary immunization is achieved with one single dose of vaccine. In order to provide long term protection, a booster should be given six to twelve months later. Based on current data, a further booster dose may be required after 10 years.

The recommended dose is 0.5 mL administered intramuscularly.

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

For information on vaccine administration see the current edition of the Canadian Immunization Guide or visit the Health Canada website.

SHAKE THE PRE-FILLED SYRINGE WELL to uniformly distribute the suspension before administration.

AVAXIM® [Hepatitis A Vaccine Inactivated] may be packaged in one of two presentations: a pre-filled syringe with a choice of two needles; or a pre-filled syringe with attached needle.

If a choice of needles is present, select a needle of appropriate length to ensure that the vaccine will be delivered intramuscularly. Remove the tip cap from the syringe, take the chosen needle from the blister pack and fix to the tip of the pre-filled syringe.

If a syringe with attached needle is present, the vaccine is ready to administer.

Aseptic technique must be used. Administer the vaccine intramuscularly. The preferred site is into the deltoid muscle or into the anterolateral aspect of the mid thigh (vastus lateralis muscle). Do not administer

in the buttocks.

Do not inject intravenously.

In exceptional circumstances (e.g., in patients with thrombocytopenia or in patients at risk of hemorrhage) the vaccine may be injected by the subcutaneous route, however this may be associated with a higher risk of local reaction including injection site nodule.

Needles should not be recapped and should be disposed of properly.

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.

PHARMACEUTICAL INFORMATION

Composition

The active ingredient is a purified and formaldehyde-inactivated hepatitis A virus. It is obtained from the GBM strain cultured on MRC-5 human diploid cells.

Each human dose (0.5 mL) contains 160 antigen units (in the absence of an international standardized reference, the antigen content is expressed using an in-house reference).

Each dose contains:

Aluminum hydroxide (expressed as Aluminum)	0.3 mg
2-Phenoxyethanol	2.5 µL
Formaldehyde	12.5 µg
Medium 199, water for injection up to	0.5 mL
Neomycin	trace amounts

AVAXIM® is a whitish, cloudy suspension.

Stability and Storage

AVAXIM® [Hepatitis A Vaccine Inactivated] should be stored at 2˚ to 8˚C (35˚ to 46˚F). DO NOT FREEZE. Discard product if exposed to freezing.

Do not use after expiration date.

AVAILABILITY OF DOSAGE FORMS

AVAXIM® [Hepatitis A Vaccine Inactivated] is supplied in packages containing either: one pre-filled single dose syringe with a choice of two needles (1 x 25G x 16 mm and 1 x 25G x 25 mm), or one pre-filled single dose syringe with attached needle.

The plunger stoppers and needle shield for the syringes supplied with this product do not contain dry natural latex rubber.

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Vaccine Information Service 1-888-621-1146 or (416) 667-2779.

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