Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

AVAXIM, suspension for injection in a pre-filled syringe Hepatitis A vaccine (inactivated, adsorbed)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Hepatitis A virus, GBM strain (inactivated)1, 2……160 EU3

1 produced in human diploid (MRC-5) cells
2 adsorbed on aluminium hydroxide, hydrated (0.3 milligrams Al^{3+})
3 ELISA Unit. In the absence of an international standardised reference, the antigen content is expressed using an in- house reference

Excipient(s) with known effect:
Ethanol anhydrous……2.5 microlitres
Phenylalanine……10 micrograms
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suspension for injection in a pre-filled syringe
Hepatitis A vaccine (inactivated, adsorbed) is a cloudy and white suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

AVAXIMis indicated for active immunisation against infection caused by hepatitis A virus in susceptible adults and adolescents of 16 years of age and above.

The use of AVAXIM should be based on official recommendations.

4.2 Posology and method of administration

Posology
The recommended dosage for subjects of at least 16 years of age is 0.5 millilitres for each injection.

Initial protection is achieved with one single dose of vaccine. Protective levels of antibody may not be reached until 14 days after administration of the vaccine.

In order to provide long-term protection, a second dose (booster) of an inactivated hepatitis A vaccine should be given. The second dose is preferably given between 6 and 12 months but may be administered up to 36 months after the first dose (see section 5.1). It is predicted that HAV antibodies persist for many years (beyond 10 years) after the second dose.

The vaccine may be used to provide the second dose (booster) in subjects from 16 years of age who received another inactivated hepatitis A vaccine (monovalent or with purified Vi polysaccharide typhoid) 6 months to up to 36 months previously.

Paediatric population
AVAXIM is not recommended for use in children of less than or equal to 15 years of age due to insufficient data on safety and efficacy.

Method ofadministration
AVAXIM should be administered by intramuscular injection in the deltoid region. AVAXIM must not be administered intradermally or intravascularly.

The vaccine should not be administered into the buttocks, due to the varying amount of fatty tissue in this region, contributing to variability in effectiveness of the vaccine.

In exceptional circumstances (e.g. in patients with thrombocytopenia or in patients at risk of haemorrhage), the vaccine may be injected by the subcutaneous route.

Precautions to be taken before handling or administering the medicinal product. For instructions on preparation of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1 or to neomycin, which may be present in the vaccine in trace amounts.
- Hypersensitivity following a previous injection of this vaccine.
- Vaccination should be delayed in subjects with an acute severe febrile illness.

4.4 Special warnings and precautions for use

As with all vaccines, appropriate medical treatment and supervision should be readily available for immediate use in case of rare anaphylactic reaction following vaccination. AVAXIM should only be given by a physician or health care worker trained in the administration of vaccines.

Syncope (fainting) can occur following, or even before, any vaccination especially in adolescents as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

AVAXIM has not been studied in patients with impaired immunity. The immune response to AVAXIM could be impaired by immunosuppressive treatment or in immunodeficiency states. In such cases, it is recommended to measure the antibody response to be sure of protection and, if possible, to wait for the end of any suppressive treatment before vaccination. Nevertheless, vaccination of subjects with chronic immunodeficiency such as HIV infection is recommended although the antibody response may be limited.

Because of the incubation period of hepatitis A, infection may be present but not clinically apparent at the time of vaccination. The effect of AVAXIM on individuals late in the incubation period of hepatitis A has not been documented.

Individuals having grown up in areas of high endemicity and/or with a history of jaundice may be immune to hepatitis A, in which case the vaccine is unnecessary. Testing for antibodies to hepatitis A prior to a decision on immunisation should be considered in such situations. If not, seropositivity against hepatitis A is not a contraindication. AVAXIM is as well tolerated in seropositive as in seronegative subjects (see Section
4.8).

AVAXIM does not provide protection against infection caused by hepatitis B virus, hepatitis C virus, hepatitis E virus or by other liver pathogens.

As no studies have been performed with AVAXIM in subjects with liver disease, the use of this vaccine in such subjects should be considered with care.

As with any vaccine, vaccination may not result in a protective response in all susceptible vaccinees.

<u>AVAXIM contains ethanol, phenylalanine, potassium and sodium</u>
AVAXIM contains 2 mg of alcohol (ethanol) in each 0.5 ml dose. The small amount of alcohol in this medicine will not have any noticeable effects.
AVAXIM contains 10 microgram phenylalanine in each 0.5 ml dose which is equivalent to 0.17 microgram/kg for a 60 kg person. Phenylalanine may be harmful for people with phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.
AVAXIM contains less than 1mmol of potassium (39 mg) and sodium (23 mg) per dose, that is to say essentially 'potassium-free' and 'sodium-free'.

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 Interaction with other medicinal products and other forms of interactions

No clinical data on concomitant administration of AVAXIM with other inactivated vaccine(s) or recombinant hepatitis B virus vaccine have been generated. When concurrent administration is considered necessary, AVAXIM must not be mixed with other vaccines in the same syringe, and other vaccines should be administered at different sites with different syringes and needles.

Seroconversion rates were not modified when AVAXIM was given at the same time as but at a different injection site to a Vi polysaccharide typhoid vaccine or a yellow fever vaccine reconstituted with a Vi polysaccharide typhoid vaccine.

Concomitant administration of immunoglobulin and AVAXIM at two separate sites may be performed.
Seroconversion rates are not modified, but antibody titres could be lower than after vaccination with AVAXIM alone. Therefore, consideration should be given to whether or not the subject is likely to be at long-term risk of exposure.

No interaction with other medicinal products is currently known.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of hepatitis A vaccine (inactivated, adsorbed) in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition or postnatal development. The potential risk for humans is unknown.
AVAXIM should not be used during pregnancy unless clearly necessary and following an assessment of the risks and benefits

Breastfeeding
The use of this vaccine is possible during breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Summary of the safety profile
In clinical trials, adverse reactions were usually mild and confined to the first few days after vaccination with spontaneous recovery.
Reactions were less frequently reported after the booster dose than after the first dose.
In subjects seropositive against hepatitis A virus, AVAXIM was as well tolerated as in seronegative subjects.

Tabulated list of adverse reactions
Adverse reaction data are derived from clinical trials and worldwide post-marketing experience.

Within each system organ class, the adverse reaction are ranked under headings of frequency, most frequent reactions first, using the following convention:

- Very common (≥1/10),
- Common (≥1/100 to <1/10),
- Uncommon (≥1/1000 to <1/100),
- Rare (≥1/10000 to <1/1000),
- Very rare (<1/10000),
- Not known (cannot be estimated from available data): the adverse reactions have been reported following the commercial use of AVAXIM based on spontaneous reporting. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency.

Adverse reactions	Frequency
Immune system disorders	
Anaphylactic reaction	Not known
Nervous system disorders	
Headache	Common
Vasovagal syncope in response to injection	Not known
Gastrointestinal disorders	
Nausea	Common
Vomiting	Common
Decreased appetite	Common
Diarrhoea	Common
Abdominal pain	Common
Skin and subcutaneous tissue disorders	
Urticaria	Not known
Rashes associated or not with pruritus	Not known
Musculoskeletal and connective tissue disorders	
Myalgia	Common
Arthralgia	Common
General disorders and administration site conditions	
Asthenia	Very common
Mild fever	Common
Mild injection site pain	Very common
Injection site erythema	Uncommon
Injection site nodule	Rare
Investigations	
Transaminases increased (mild and reversible)	Rare

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

A few cases of overdose have been reported with AVAXIM, without specific adverse event.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Viral vaccine, ATC Code: J07BC02

AVAXIM confers immunity against hepatitis A virus by inducing antibody titres greater than those obtained after passive immunisation with immunoglobulin. Antibody appears shortly after the first injection and 14 days after vaccination more than 90% of immunocompetent subjects are seroprotected (titre above 20 mIU/millilitre).

One month after the first injection, almost 100% of subjects have antibody titres above 20mIU/millilitre. Serological data show continuing protection against hepatitis A for up to 36 months in subjects who responded to the first dose. In a study of 103 healthy adults who were followed serologically for three years after the first injection of AVAXIM, 99% still had at least 20 mIU/ml anti HAV antibody at month 36.

The long-term persistence of protective antibody levels to hepatitis A virus after a second dose (booster) of AVAXIM has not been fully evaluated. Nevertheless, available data (antibody titres obtained two years after the second dose) suggest that anti-HAV antibodies persist beyond 10 years after the second dose in healthy individuals.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of acute toxicity, repeated dose toxicity, local tolerance and hypersensitivity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

2-phenoxyethanol
Formaldehyde
Medium 199 Hanks *
Water for injections
Hydrochloric acid and sodium hydroxide for pH adjustment

*Medium 199 Hanks is a complex mixture of amino acids (including phenylalanine), mineral salts, vitamins and other components.

6.2 Incompatibilities

In the absence of compatibility studies, the vaccine must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze. If frozen, the vaccine should be discarded.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

0.5 ml of suspension in pre-filled syringe (type I glass) with a plunger-stopper (bromochlorobutyl or chlorobutyl or bromobutyl) and attached needle and needle-shield (natural rubber or polyisoprene). Packs of 1, 5, 10 and 20 syringes.

0.5 ml of suspension in pre-filled syringe (type I glass) with a plunger-stopper (bromochlorobutyl or chlorobutyl or bromobutyl), without needle. Packs of 1, 5, 10 and 20 syringes.

0.5 ml of suspension in pre-filled syringe (type I glass) with a plunger-stopper (bromochlorobutyl or chlorobutyl or bromobutyl), with 1 or 2 separate needles (for each syringe). Packs of 1 and 10 syringes.

Not all pack sizes and presentations may be marketed.

6.6 Special precautions for disposal and other handling

For needle free syringes, the needle should be pushed firmly on to the end of the prefilled syringe and rotated through 90 degrees.

Shake before injection to obtain a homogeneous suspension. The vaccine should be visually inspected before administration for any foreign particulate matter.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Sanofi Pasteur
14 Espace Henry Vallée
69007
Lyons
France

8 MARKETING AUTHORISATION NUMBER

PA2131/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 February 1997

Date of last renewal: 30 April 2006

10 DATE OF REVISION OF THE TEXT

November 2021