SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AVAXIM 160 U, suspension for injection in prefilled syringe

Hepatitis A vaccine (inactivated, adsorbed)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 ml) contains:

Hepatitis A virus, GBM strain* (inactivated)**..... 160 ELISA units***

* Cultured on MRC-5 human diploid cells

** Adsorbed on hydrated aluminium hydroxide (0.3 milligrams of Al)

*** In the absence of an international standardised reference, the antigen content is expressed using an in-house reference.

Excipient(s) with known effect:

Less than 1 mmol of sodium and less than 1 mmol of potassium per dose

Ethanol.....2.5 microlitres

Phenylalanine..... 10 micrograms

Per 0.5 ml dose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection in a prefilled syringe.

The hepatitis A vaccine (inactivated, adsorbed) is a turbid and whitish suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This vaccine is indicated for active immunisation against infection caused by the hepatitis A virus in adolescents from 16 years of age and in adults.

This vaccine should be administered in accordance with official recommendations.

4.2 Posology and method of administration

Posology

The recommended dosage for subjects from 16 years of age is 0.5 ml.

The initial protection is obtained after one single injection.

In order to obtain a long-term protection against infections caused by the Hepatitis A virus, in adolescents from 16 years of age and in adults, a second dose (booster) should be administered, preferably between 6 and 12 months after the first vaccination and can be administered up to 36 months after the first vaccination (see section 5.1). It is estimated that anti-VHA antibodies persist several years (beyond 10 years) after the second dose (booster).

This vaccine can also be administered as a booster dose of the hepatitis A vaccination in subjects from 16 years of age who received a first injection with the combined typhoid fever (Vi purified polysaccharide) and hepatitis A (inactivated) vaccine between 6 and 36 months earlier.

Paediatric population

Not applicable.

Method of administration

- This vaccine must be administered by the intramuscular route (IM). The recommended injection site is the deltoid region.
- In exceptional cases, the vaccine may be administered by the subcutaneous route in patients with thrombocytopenia or in patients at risk of haemorrhage.
- The vaccine should not be administered into the buttocks because of the varying amount of fat tissue in this region, that may contribute to variability in effectiveness of the vaccine.
- Do not inject by the intravascular route: ensure that the needle does not penetrate a blood vessel.
- Do not inject by the intradermal route.
- See section 6.6 for the instructions on preparation.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients or to neomycin (that may be present as traces in each dose due to its use during the manufacturing process).
- Hypersensitivity following a previous injection of this vaccine.
- Vaccination should be postponed in case of severe acute febrile illness.

4.4 Special warnings and precautions for use

- As with all injectable vaccines, available appropriate medical treatment and subject monitoring are recommended in case of an anaphylactic reaction after vaccine administration.
- AVAXIM 160 U has not been studied in patients with impaired immunity.
- Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection, especially in adolescents. This may be accompanied by several neurological signs such as transient sight disorders, paraesthesia and tonic-clonic limb movements during the recovery phase. It is important that procedures be in place to avoid any injury from faints.
- Immunosupressive treatment or immunodeficiency may induce a decrease in the immune response to the vaccine.
  It is then recommended to wait until the end of treatment before vaccinating or to make sure the subject is well protected. Nevertheless, vaccination of subjects with chronic immunodeficiency such as HIV infection is recommended even though the antibody response might be limited.
- Because of the incubation period of hepatitis A, infection may already be present, although asymptomatic, at the time of vaccination. The effect of administering AVAXIM 160 U during the incubation period of hepatitis A has not been documented. In such a case, vaccination may have no effect on the development of hepatitis A.
- The use of this vaccine in subjects with liver disease should be considered with caution, as no studies have been performed in such subjects.
- As with all vaccines, a protective immune response may not be obtained in all vaccinees.
- The vaccine does not protect against infection caused by hepatitis B, hepatitis C or hepatitis E viruses, or by other known liver pathogens.
- **AVAXIM 160 U contains ethanol, phenylalanine, potassium and sodium**
  - AVAXIM 160 U contains small amounts of ethanol (alcohol), less than 100 mg per dose.
  - AVAXIM 160 U contains 10 micrograms of phenylalanine in each 0.5 ml dose, which is equivalent to 0.17 micrograms/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 160 U contains less than 1 mmol of potassium (39 mg) and sodium (23 mg) per dose, that is to say essentially “potassium-free” and “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of immunoglobulins and this vaccine in two separate sites may be performed. Seroprotection rates are not modified but antibody titres may be lower than those obtained when the vaccine is administered alone.

When concomitant administration is deemed necessary, AVAXIM 160 U must not be mixed with other vaccines in a same syringe: the other vaccines must be administered in separate sites using separate syringes and needles.

As the vaccine is inactivated, association with other inactivated vaccine(s) in a separate injection site does not generally result in any interaction.

This vaccine can be administered simultaneously, but in two separate sites, with a typhoid polysaccharide vaccine (Typhim Vi) without modification of the immune response to either antigen.

This vaccine can be administered simultaneously, but in two separate sites, with the live yellow fever vaccine.

This vaccine can be used as a booster dose in subjects who have received primary vaccination with another inactivated hepatitis A vaccine.

4.6 Fertility, pregnancy and lactation

Pregnancy

No reliable data are available on teratogenesis in animals.

To date, there are no sufficiently relevant clinical data available to assess a potential vaccine-related malformation or foetotoxic effect of the hepatitis A vaccine, when it is administered during pregnancy.

As a precautionary measure, it is preferable not to use this vaccine during pregnancy except in case of a major contamination risk.

Breast-feeding

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

4.7 Effects on ability to drive and use machines

The effects on the ability to drive and use machines have not been studied.

4.8 Undesirable effects

The undesirable effects are derived from clinical studies and worldwide post-marketing experience.

The undesirable effects are ranked under headings of frequency using the following convention:

Very common (≥ 1/10)
Common (≥ 1/100 and < 1/10)
Uncommon (≥ 1/1,000 and < 1/100)
Rare (≥ 1/10,000 and < 1/1,000)
Very rare (< 1/10,000)
Not known: cannot be estimated from available data.

Nervous system disorders

Common: cephalalgia.
Not known: vasovagal syncope in response to injection.

Gastrointestinal disorders

Common: nausea, vomiting, appetite decrease, diarrhoea, abdominal pain.

Skin and subcutaneous tissue disorders

Not known: urticaria, rash associated or not with pruritus.

Musculoskeletal and connective tissue disorders

Common: myalgia, arthralgia.

General disorders and administration site conditions

Very common: asthenia, mild injection site pain.
Common: mild fever.
Uncommon: injection site erythema.

Rare: injection site nodule.

Investigations

Rare: increase in serum transaminases (mild and transient).

The reactions were less frequently reported after the booster injection than after the first dose.

In subjects seropositive against hepatitis A virus, this vaccine was as well tolerated as in seronegative subjects.

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 the national reporting system: "Agence nationale de sécurité du médicament et des produits de santé (ANSM) et réseau des Centres Régionaux de Pharmacovigilance - Site internet: www.signalement-sante.gouv.fr".

4.9 Overdose

A few cases of overdose have been reported with AVAXIM 160 U, with no specific undesirable effects.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccine against hepatitis A, ATC code: J07BC02.

This vaccine is prepared from hepatitis A virus cultured, purified and then inactivated by formaldehyde. It confers immunity against hepatitis A virus by inducing a higher antibody response than that obtained after passive immunisation with immunoglobulins. The antibodies appear soon after the first injection, and 14 days after vaccination, more than 90% of immunocompetent subjects are seroprotected (titres above 20 mIU/ml).

One month after the first injection, almost 100% of subjects have titres higher than 20 mIU/ml. Immunity may persist up to the 36th month. In a study with 103 healthy subjects whose serology levels were monitored for 3 years after the first injection of AVAXIM 160 U, 99% still had, by the 36th month, antibody titres of at least 20 mIU/ml against the hepatitis A virus.

Long-term persistence of a protective antibody level against the hepatitis A virus after a second dose (booster) of AVAXIM 160 U is not currently established. However, the available data suggest that the antibodies against the hepatitis A virus persist beyond 10 years after the second dose in healthy people.

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, ethanol, formaldehyde, and Hanks 199 medium*, water for injections, polysorbate 80, hydrochloric acid and sodium hydroxide for pH adjustment.

*Hanks 199 medium (without phenol red) is a complex mixture of amino acids (including phenylalanine), mineral salts, vitamins, and other components, including potassium.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product 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.

Keep in the original packaging, protected from light.

6.5 Nature and contents of container

0.5 ml of suspension in prefilled syringe (type I glass) with a plunger stopper (bromochlorobutyl or chlorobutyl or bromobutyl), and an attached needle. Box of 1, 5, 10 or 20.

0.5 ml of suspension in prefilled syringe (type I glass) with a plunger stopper (bromochlorobutyl or chlorobutyl or bromobutyl), without needle. Box of 1 or 10.

0.5 ml of suspension in prefilled syringe (type I glass) with a plunger stopper (bromochlorobutyl or chlorobutyl or bromobutyl), with 1 or 2 separate needles. Box of 1 or 10.

All pack sizes may not be marketed.

6.6 Special precautions for disposal and other handling

Shake before injection, until a homogenous suspension is obtained.

For the syringes without attached needles, the separate needle should be fitted firmly to the syringe, rotating it by one quarter turn.

The vaccine must be visually inspected before administration to verify the absence of foreign particles.

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

7. MARKETING AUTHORISATION HOLDER

SANOFI PASTEUR
14 ESPACE HENRY VALLÉE
69007 LYON
FRANCE

8. MARKETING AUTHORISATION NUMBER(S)

- 34009 341 665 2 5: 0.5 ml of suspension in prefilled syringe (type I glass) with a plunger stopper (bromochlorobutyl or chlorobutyl or bromobutyl), and an attached needle. Box of 1.
- 34009 341 666 9 3: 0.5 ml of suspension in prefilled syringe (type I glass) with a plunger stopper (bromochlorobutyl or chlorobutyl or bromobutyl), and an attached needle. Box of 5.
- 34009 341 667 5 4: 0.5 ml of suspension in prefilled syringe (type I glass) with a plunger stopper (bromochlorobutyl or chlorobutyl or bromobutyl), and an attached needle. Box of 10.
- 34009 341 668 1 5: 0.5 ml of suspension in prefilled syringe (type I glass) with a plunger stopper (bromochlorobutyl or chlorobutyl or bromobutyl), and an attached needle. Box of 20.
- 34009 370 816 5 8: 0.5 ml of suspension in prefilled syringe (type I glass) with a plunger stopper (bromochlorobutyl or chlorobutyl or bromobutyl) without needle. Box of 1.

- 34009 370 817 1 9: 0.5 ml of suspension in prefilled syringe (type I glass) with a plunger stopper (bromochlorobutyl or chlorobutyl or bromobutyl) without needle. Box of 10.
- 34009 370 818 8 7: 0.5 ml of suspension in prefilled syringe (type I glass) with a plunger stopper (bromochlorobutyl or chlorobutyl or bromobutyl) with one separate needle. Box of 1.
- 34009 370 819 4 8: 0.5 ml of suspension in prefilled syringe (type I glass) with a plunger stopper (bromochlorobutyl or chlorobutyl or bromobutyl) with one separate needle. Box of 10.
- 34009 370 820 2 0: 0.5 ml of suspension in prefilled syringe (type I glass) with a plunger stopper (bromochlorobutyl or chlorobutyl or bromobutyl) with two separate needles. Box of 1.
- 34009 370 821 9 8: 0.5 ml of suspension in prefilled syringe (type I glass) with a plunger stopper (bromochlorobutyl or chlorobutyl or bromobutyl) with two separate needles. Box of 10.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[to be completed later by the holder]

10. DATE OF REVISION OF THE TEXT

[to be completed later by the holder]

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

SECTION II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

A.1. Name and address of the manufacturer(s) of the biological active substance(s)

SANOFI PASTEUR
1541 AVENUE MARCEL MERIEUX
69280 MARCY L'ETOILE
FRANCE

A.2. Name and address of the manufacturer(s) responsible for batch release

SANOFI PASTEUR
1541 AVENUE MARCEL MERIEUX
69280 MARCY L'ETOILE
FRANCE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

List I.

- Official batch release

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION HOLDER

- **Periodic Safety Update Reports (PSUR)**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

Not applicable

F. QUALITATIVE AND QUANTITATIVE COMPOSITION IN EXCIPIENTS

For one 0.5 ml dose:

2-Phenoxyethanol solution ..... 2.5 microlitres

Ethanol ..... 2,5 microlitres

Formaldehyde ..... 12.5 micrograms

Hanks 199 medium* ..... qs 0.5 ml

* Hanks 199 medium (without phenol red) is a complex mixture of amino acids (including phenylalanine), mineral salts, vitamins, and other components, including potassium, supplemented with polysorbate 80 and diluted in water for injections and with a pH that has been adjusted with hydrochloric acid or sodium hydroxide.

SECTION IIIA

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND ON THE IMMEDIATE PACKAGING

NATURE/TYPE OUTER PACKAGING OR PRIMARY PACKAGING

Outer packaging

1. NAME OF THE MEDICINAL PRODUCT

AVAXIM 160 U, suspension for injection in prefilled syringe

Hepatitis A vaccine (inactivated, adsorbed)

2. STATEMENT OF ACTIVE SUBSTANCES

One dose (0.5 ml) contains:

Hepatitis A virus, GBM strain* (inactivated) ** ..... 160 ELISA units***

* Cultured on MRC-5 human diploid cells

** Adsorbed on hydrated aluminium hydroxide (0.3 milligrams of Al^{3+})

*** In the absence of an international standardised reference, the antigen content is expressed using an in-house reference.

3. LIST OF EXCIPIENTS

2-phenoxyethanol, ethanol*, formaldehyde, Hanks 199 medium without phenol red (a complex mixture of amino acids (including phenylalanine*), mineral salts, vitamins, and other components, including potassium) supplemented with polysorbate 80 and diluted in water for injections, with a pH adjusted with hydrochloric acid* or sodium hydroxide*.

* Read the package leaflet for more information.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection (0.5 ml) in a prefilled syringe <without needle> <with attached needle> <with> <one> <two> <separate needles>. Box of 1, 5, 10, or 20.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular route (IM).

Shake well before use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Not applicable.

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).

Do not freeze.

If frozen, the vaccine should be discarded.

Keep in the original packaging, protected from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Holder

SANOFI PASTEUR
14 ESPACE HENRY VALLÉE
69007 LYON
FRANCE

Distributor

SANOFI PASTEUR EUROPE
14 ESPACE HENRY VALLÉE
69007 LYON
FRANCE

12. MARKETING AUTHORISATION NUMBER(S)

Authorised Medicinal product No:

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

List I

15. INSTRUCTIONS ON USE

Not applicable.

16. INFORMATION IN BRAILLE

[Comply with the decision of May 7, 2008 taken pursuant to article R. 5121-138 of the Public Health Code, published in the OJ of May 22, 2008]

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}

SN: {number}

PICTOGRAM TO APPEAR ON THE OUTER PACKAGING OR, IN THE ABSENCE OF OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Pictogram on teratogenic or foetotoxic effects

Where applicable, the pictogram mentioned in section III of article R. 5121-139 of the Public Health Code (teratogenic or foetotoxic effects) must be affixed in compliance with the implementing decree provided for in the same article.

Pictogram on effects on the ability to drive

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

NATURE/TYPE BLISTERS / STRIPS

Not applicable.

1. NAME OF THE MEDICINAL PRODUCT

Not applicable.

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Not applicable.

3. EXPIRY DATE

Not applicable.

4. BATCH NUMBER

Not applicable.

5. OTHER

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

NATURE/TYPE SMALL IMMEDIATE PACKAGING

Prefilled syringe

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

AVAXIM 160 U, suspension for injection in prefilled syringe

Hepatitis A vaccine (inactivated,

adsorbed) IM route

2. METHOD OF ADMINISTRATION

Not applicable.

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Batch {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose = 0.5 ml

6. OTHER

Not applicable.