ANNEX I

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^{3+})

*** 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 sodium and less than 1 mmol 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 aged 16 years and over and in adults.

This vaccine should be administered in accordance with official recommendations.

4.2 Posology and method of administration

Posology

The recommended dose for subjects aged 16 years and over 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 aged 16 years and over 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–hepatitis A virus (HAV) 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 aged 16 years and over 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 (IM) route. 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, which 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 (which 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.

Immunosuppressive 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 2 mg of alcohol (ethanol) in each 0.5 mL dose. The small amount of alcohol in this medicinal product will not have any noticeable effects.

Avaxim 160 U contains 10 micrograms phenylalanine in each 0.5 mL dose, which is equivalent to 0.17 micrograms/kg for a 60 kg person. Phenylalanine may be harmful to 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 potassium (39 mg) and less than 1 mmol 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 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 fetotoxic 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

Summary of tolerance profile

During clinical studies, adverse reactions were generally moderate and limited to the first days following vaccination with spontaneous regression.

The reactions were less frequently reported after administration of 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

The adverse reactions are derived from clinical studies and worldwide post-marketing experience.

The adverse reactions are ranked under headings of frequency using the following convention:

Very common	(≥ 1/10)
Common	(≥ 1/100 to < 1/10)
Uncommon	(≥ 1/1 000 to < 1/100)
Rare	(≥ 1/10 000 to < 1/1 000)
Very rare	(< 1/10 000)

Not known (cannot be estimated from available data): adverse reactions were spontaneously reported after the marketing of Avaxim 160 U. Given that these reactions were reported voluntarily by a population of unknown size, it is not possible to accurately 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
Decrease in appetite	Common
Diarrhoea	Common
Abdominal pain	Common
Skin and subcutaneous tissue disorders	
Urticaria	Not known
Rash 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
Slight fever	Common
Mild injection site pain	Very common
Injection site erythema	Uncommon
Injection site nodule	Rare
Investigations	
Increased serum transaminases (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 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 adverse reactions.

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 must 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 (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 (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 (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 must 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 (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 (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 (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 (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 (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 (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 (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 (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 (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 (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.

GENERAL CLASSIFICATION FOR SUPPLY

List I