1. NAME OF THE MEDICINAL PRODUCT

AVAXIM 80 U PEDIATRIC

Suspension for injection in pre-filled syringe Hepatitis A vaccine (inactivated, adsorbed)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Hepatitis A virus, GBM strain* (inactivated) ** …… 80 ELISA unit***
for one dose of 0.5 mL
* Cultured on MRC5 human diploid cells.
** Adsorbed on hydrated aluminium hydroxide (0.15 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 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 pre-filled syringe.
The hepatitis A vaccine (inactivated, adsorbed) is a turbid and whitish suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AVAXIM 80 U PEDIATRIC is indicated for active immunisation against infection caused by hepatitis A virus in children aged from 12 months to 15 years inclusive, who are at risk either of contaminating or spreading infection or of a life-threatening disease if infected.
Transmission of the hepatitis A virus usually occurs through the consumption of contaminated water or food. Persons in contact with contaminated subjects are usually infected through oro- fecal routes.
The possibility of transmission through the blood or by sexual contacts (oral-anal relations) has also been proven.
Potential candidates for the vaccine are:
– 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.

4.2 Posology and method of administration

Posology

Paediatric population

- Primary-vaccination

Primary vaccination is achieved with one vaccine dose of 0.5 mL.

- Booster

One booster dose of 0.5 mL is recommended in order to provide long-term protection. This booster dose will preferably be administered 6 to 36 months following the primary vaccination dose, but administration will be possible until 7 years after this primary vaccination.

Available data on vaccination with AVAXIM 80 U PEDIATRIC show that after the two doses of the initial vaccination schedule, no other booster vaccination is necessary in immunocompetent individuals, which is in agreement with the official recommendations.

Method of administration

This vaccine must be administered by the intramuscular route. The recommended injection site is the deltoid region.
In exceptional cases, the vaccine may be administered by the subcutaneous route in patients suffering from thrombocytopaenia 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.

4.3 Contraindications

- Hypersensitivity to the active substance, to one of the excipients, 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.

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.

AVAXIM 80 U PEDIATRIC has not been studied in patients with impaired immunity.

The immune response to the vaccine may be impaired by immunosuppressive treatment or immunodeficiency. In such cases it is recommended to wait for 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 80 U PEDIATRIC 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, vaccination may not induce a protective response in some vaccinees.

The vaccine does not protect against infection caused by hepatitis B virus, hepatitis C virus, hepatitis E virus or by other known liver pathogens.

AVAXIM 80 U PEDIATRIC, suspension for injection in prefilled syringe contains ethanol, phenylalanine, potassium and sodium

- AVAXIM 80 U PEDIATRIC contains small amounts of ethanol (alcohol), less than 100

mg per dose.

- AVAXIM 80 U PEDIATRIC 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 80 U PEDIATRIC 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

The simultaneous administration of immunoglobulins with this vaccine in two different injection sites may be performed. The seroprotection rates are not modified, but the antibody titres may be lower than those obtained when the vaccine is administered alone.

In case of simultaneous administration, this vaccine must not be mixed with other vaccines in the same syringe. The vaccine may be administered simultaneously, in two different injection sites, with the routine booster vaccine of the child during the second year of life, i.e. various vaccines containing one or more of following valences: diphtheria, tetanus, pertussis (acellular or whole cells), *Haemophilus influenzae* of type b and inactivated or oral poliomyelitis.

This vaccine can be administered simultaneously, but at two different injection sites, with a vaccine against measles, mumps and rubella.

This vaccine can be used as a booster in subjects previously vaccinated with another inactivated Hepatitis A vaccine.

4.6 Pregnancy and lactation

Pregnancy

No relevant teratogenic data on animal are available.
In humans, up to now, the data is inadequate to assess teratogenic or foetotoxic risk of the vaccine against Hepatitis A when 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.

Breastfeeding

The effect of administration of AVAXIM 80U Pediatric during lactation has not been assessed. As AVAXIM 80U Pediatric is inactivated, any risk to the mother or the infant is improbable. The benefits versus the risks of administering AVAXIM 80U Pediatric during lactation should carefully be evaluated.

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

a. Summary of the safety profile

More than 6200 children aged from 12 months to 15 years (around 7000 administered doses) were vaccinated with AVAXIM 80 U PEDIATRIC during clinical trials.
Most undesirable effects were moderate and limited to the first few days following vaccination with spontaneous recovery. Reactions were more rarely reported after the booster dose than after the first dose.
However, as with all pharmaceuticals, expanded commercial use of the vaccine might reveal rarer undesirable effects.

b. Tabulated list of adverse reactions

The undesirable effects are derived from clinical studies and worldwide post-marketing experience.
In each System Organ Class, the undesirable effects are ranked under headings of frequency, the most common reactions coming first, using the following convention:

Very common (≥ 1/10)
Common (≥ 1/100, < 1/10)
Uncommon (≥ 1/1 000, < 1/100)
Rare (≥ 1/10 000, < 1/1000)
Very rare (< 1/10 000)
Not known: cannot be estimated from the available data.

The table below summarize the frequencies of the adverse reactions that were recorded after the first dose, after the booster dose or after any dose of AVAXIM 80 U PEDIATRIC.

Adverse reactions	**Frequency after the primary dose**	**Frequency after the booster dose**	**Frequency after any dose**
Metabolism and nutrition disorders			
Appetite decrease	Common	Common	Common
Psychiatric disorders			
Abnormal crying Irritability Insomnia	Very common Common Common	Uncommon Common Common	Very common Common Common
Nervous system disorders			
Cephalalgia Vasovagal syncope in response to injection	Common Not known	Common Not known	Very common Not known
Gastrointestinal disorders			

Adverse reactions	Frequency after the primary dose	Frequency after the booster dose	Frequency after any dose
Abdominal pain	Common	Common	Common
Diarrhoea	Common	Common	Common
Nausea	Common	Common	Common
Vomiting	Common	Common	Common
Skin and subcutaneous tissue disorders			
Rash	NR*	Uncommon	Uncommon
Urticaria	Uncommon	NR*	Uncommon
Musculoskeletal and connective tissue disorders			
Arthralgia	Common	Uncommon	Common
Myalgia	Common	Common	Common
General disorders and administration site conditions			
Local reactions			
Pain at the injection site	Very common	Common	Very
Redness at the injection site	Common	Common	common
Induration or oedema at the injection site	Common	Common	Common
Haematoma at the injection site	Common	Uncommon	Common
Systemic reactions			Common
Malaise	Common	Common	
Fever	Common	Common	Very
Asthenia or somnolence			common
			Common
			Common

* Not reported during clinical studies

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.

4.9 Overdose

An overdose is unlikely to provoke any harmful effects.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Viral vaccine, ATC code: J07B C02

This vaccine is prepared from hepatitis A virus cultured, harvested, purified and then inactivated by formaldehyde.
It confers immunity against hepatitis A virus (HAV) by inducing antibody titres longer lasting and higher than those obtained after passive immunisation with immunoglobulins. This vaccine has been demonstrated to elicit protective anti-HAV antibody titres (≥ 20 mIU/mL) within two weeks following the injection in over 95% of individuals and in 100% of individuals before the booster dose administered 6 months after the first dose.

A study conducted in Argentina (an area of intermediate endemicity for hepatis A) enabled the evaluation of long term persistence of anti-HAV antibodies in children aged 12 months to 47 months vaccinated with 2 doses of Avaxim 80 U Pediatric 6 months apart. The results show a persistence of the antibodies until 14-15 years at levels considered as protective and do not suggest the need for new administration of the vaccine.
A mathematical model using the available data from this study until 14-15 years after administration of the 2 doses of Avaxim 80 U Pediatric predicts a persistence of the protective anti-HAV antibodies for at least 30 years in 87.5% (CI 95%: 74.1; 94.8) of these children.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

2-Phenoxyethanol, ethanol, formaldehyde and Hanks Medium 199* , 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 pharmaceutical 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.
Keep in the original packaging, protected from light.

6.5 Nature and contents of container

AVAXIM 80U Pediatric is a suspension for injection supplied in packages containing one prefilled single dose syringe (0.5ml) with attached needle.

6.6 Special precautions for disposal and other handling

Shake before injection, until a homogenous suspension is obtained.
The vaccine must be visually inspected before administration to verify the absence of foreign particles.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER SANOFI PASTEUR

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8. DATE OF REVISION OF THE TEXT

May 2020
(CCDS v11 12 13 based on FR SmPC Jul 2019)