SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One 0.5 millilitre dose contains:

Hepatitis A virus, GBM strain (inactivated) [1, 2]……80EU[3]

[1] produced in human diploid (MRC-5) cells
[2] adsorbed on aluminium hydroxide, hydrated (0.15 milligrams Al^{3+})
[3] ELISA Unit. In the absence of an international standardised reference, the antigen content is expressed using an in- house reference

Residues of clinical relevance
The vaccine may contain traces of neomycin, which is used during the manufacturing process (see section 4.3).

Excipient(s) with known effect (see Section 4.4):
Phenylalanine……10 micrograms

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Active immunisation against infection caused by hepatitis A virus in children from 1 year up and including 15 years of age.

The use of Avaxim Junior should be based on official recommendations.

4.2 Posology and method of administration

Posology

The primary vaccination consists of one 0.5 ml dose of vaccine. Initial protection starts within 2 weeks after administration.

In order to provide a long-term protection, a second dose (booster) of vaccine is recommended. This booster dose should be given between 6 months to 10 years after the first dose (see section 5.1).In line with WHO recommendation, in a setting transitioning from high to intermediate endemicity, in childhood immunization programmes either a single-dose or two-dose schedule (primary vaccination and booster) can be used.

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

Method of administration

Avaxim Junior should be administered intramuscularly in the deltoid area in older children and adolescents, and anterolateral area of the thigh in young children.

Avaxim Junior must not be administered intradermally or intravascularly: ensure that the needle does not penetrate a blood vessel.

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.

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.

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

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.

Anaphylactic reaction
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 Junior should only be given by a physician or health care worker trained in the administration of vaccines.

Anxiety-related reactions
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 and symptoms 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.

Impaired immunity
Avaxim Junior has not been studied in patients with impaired immunity. The immune response to the vaccine 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.

Vaccination during incubation period
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 Junior on individuals during the late stage of the incubation period of hepatitis A has not been documented. In such a case, vaccination may not modify the course of infection.

Vaccination of already immunized subjects
Individuals who have grown up in areas of high hepatitis A 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 could be considered in such situations. In the absence of testing, seropositivity against hepatitis A is not a contraindication to vaccination.

Protection
Avaxim Junior does not provide protection against infection caused by hepatitis B virus, hepatitis C virus, hepatitis E virus or by other liver pathogens.
As with any vaccine, vaccination may not result in a protective response in all susceptible vaccinees.

Avaxim Junior contains phenylalanine, ethanol, potassium and sodium
- Avaxim Junior 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 Junior 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 Junior contains less than 1mmol of potassium (39 mg) and sodium (23 mg) per dose, that is to say it is essentially 'potassium-free' and 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Separate injection sites and separate syringes must be used in case of concomitant administration with other medicinal products.

The vaccine may be administered simultaneously with vaccines containing one or more of following valences: diphtheria, tetanus, pertussis (acellular or whole cells), *Haemophilus influenzae* of type b, inactivated or oral poliomyelitis, measles, mumps and rubella.

Concomitant administration of immunoglobulin has been studied with Avaxim (corresponding to 160U) in adults, but not with Avaxim Junior in children. The results from Avaxim in adults suggest that concomitant administration of immunoglobulin and Avaxim Junior at two separate sites may be performed. Seroconversion rates are not modified, but antibody titres could be lower than after vaccination with Avaxim Junior alone.

No interaction with other medicinal products is currently known.

4.6 Fertility, pregnancy and lactation

Pregnancy
Limited data are available on the use of Avaxim vaccines in pregnant women. No animal reproductive studies have been conducted. However, no conclusions can be drawn regarding whether or not Avaxim Junior is safe for use during pregnancy.
Avaxim Junior should be used during pregnancy only if the potential benefits to the mother outweigh the potential risks, including those to the foetus.

Breast-feeding
Avaxim Junior can be used during breastfeeding.

Fertility
Avaxim Junior has not been evaluated for impairment of male or female fertility.

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

This summary of safety profile is based on pooled analysis that integrated data from 5458 children aged from 12 months through 15 years of age, who received at least one injection of Avaxim Junior during clinical trials.

Most undesirable effects were 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.

In subjects seropositive against hepatitis A virus, Avaxim Junior was as well tolerated as in seronegative subjects.

Tabulated list of adverse reactions

Adverse event information is derived from clinical studies and worldwide post-marketing experience. Within each system organ class the adverse events are ranked under headings of frequency, using the following CIOMS frequency rating:

- Very common ≥10%;
- Common ≥ 1 and <10%;
- Uncommon ≥0.1 and <1%;
- Rare ≥0.01 and < 0.1%;
- Very rare < 0.01%;
- Not known (cannot be estimated from available data).

Adverse reactions	**Frequency after any dose**
Immune system disorders	
Anaphylactic reaction	Not known
Metabolism and nutrition disorders	
Appetite decrease	Common
Psychiatric disorders	
Abnormal crying	Very common
Irritability	Common
Insomnia	Common
Nervous system disorders	
Headache	Very common
Vasovagal syncope in response to injection	Not known
Convulsions with or without fever	Not known
Gastrointestinal disorders	
Abdominal pain	Common
Diarrhoea	Common
Nausea	Common
Vomiting	Common
Skin and subcutaneous tissue disorders	
Rash	Uncommon
Urticaria	Uncommon
Musculoskeletal and connective tissue disorders	
Arthralgia	Common
Myalgia	Common

Adverse reactions	Frequency after any dose
General disorders and administration site conditions	
Injection site pain	Very common
Malaise	Very common
Pyrexia	Common
Injection site erythema	Common
Asthenia or drowsiness	Common
Injection site induration or oedema	Common
Injection site haematoma	Common

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 listed in Appendix V.

4.9 Overdose

There have been reports of administration of higher than recommended doses of Avaxim Junior. Adverse events reported following overdosage were similar to those reported with normal vaccine administration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Viral vaccine, ATC Code: J07BC02

Avaxim Junior confers immunity against hepatitis A virus (HAV) by inducing anti-HAV antibody titres longer lasting and higher than those obtained after passive immunisation with immunoglobulins.

Immune response after the first dose and the booster dose

The vaccine has been demonstrated to elicit protective anti-HAV antibody titres (≥ 20 mIU/mL) within two weeks following the first injection in over 95% of individuals and in almost all individuals before the booster dose administered 6 months after the first dose.

Pooled immunogenicity analysis was conducted on 5 clinical trials (using the same titration method) involving more than 1,800 subjects aged from 1 year through 15 years of age. Analysis per age group showed that 2-4 weeks following the first injection, protective anti-HAV antibody titres were reached in 99.1% of subjects aged 12-23 months, 97.9% of subjects from 2 to 11 years, and 95.3% of subjects from 12 to 15 years.

Anti-HAV titers are reinforced after a booster dose. In the same pooled analysis, the Geometric Mean Titers (GMTs) were 210 mIU/mL (95% CI: 193; 227) before and 6,560 mIU/mL (95% CI: 6,210; 6,929) after the booster injection administered 6 months after the first injection, corresponding to a GMT Ratio of 30.5 (95% CI: 28.5; 32.7).
The response after 2 doses of vaccine was the highest in the youngest groups of subjects, i.e., 6805 mIU/mL (95%CI: 6263; 7394) in 12-23 months, 6903 mIU/mL (95%CI: 6393; 7453) in the 2-11 years old vs 4651 mIU/mL (95%CI: 3848; 5620) in the 12-15 years old.

Persistence of the immune response

Two studies were conducted in Argentina (an area of intermediate endemicity for hepatitis A) to evaluate hepatitis A antibody long term persistence.

One study (HAF83) was conducted in children (N=54) aged 12 through 47 months vaccinated with 2 doses of the vaccine 6 months apart. The results showed a persistence of the antibodies for a period up to 14-15 years at levels considered as protective and do not suggest a need for new administration of the vaccine.

A statistical model using the available data from this study until 14-15 years after the administration of the 2 doses of the vaccine predicts a persistence of the protective anti-HAV antibodies for at least 30 years in 87.5% of these children (estimated prediction within the 95% confidence interval CI [74.1; 94.8]).

Another non-interventional study (HAF82) was conducted with children aged between 11 and 23 months at the time of inclusion. All children had received routine vaccination with 1 dose (Group 1: N = 436) or 2 doses (Group 2: N = 108) of hepatitis A vaccine. After 10 years of follow-up, all remaining subjects showed seroprotective level (anti-HAV antibodies concentration ≥ 3 mIU/mL, using ECLIA) in both groups. Statistical modelling based on the HAF82 results including a natural boosting effect predicted similar persistence of protective anti-HAV antibody titers up to 30 years, following administration of 1 or 2 doses in over 89% with 95% CI [80; 96] to 85% with 95% CI [70; 95] of subjects respectively.

Impact of mass vaccination on disease incidence

A study was conducted in Minsk City, Belarus to assess the effectiveness of hepatitis A vaccination. During a 4-year vaccination campaign, a cohort of 66,795 adults and children received 2 doses of either Avaxim 160U or Avaxim Junior (95%) or another hepatitis A vaccine (5%). During this time, hepatitis A incidence in the 63,900 vaccinated children from 1 to 14 years was 20-fold lower than the incidence in unvaccinated children (0.3 cases/10,000 vs 5.98/10,000; odds ratio = 0.05, 95% CI: 0.012-0.202), demonstrating vaccination effectiveness of 95%. In addition, during the same period, the incidence in all age groups, including those non-vaccinated also markedly decreased, suggesting a herd effect.

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 anhydrous
Formaldehyde
Medium 199 Hanks*
Water for injections
Polysorbate 80
Hydrochloric acid and sodium hydroxide for pH adjustment

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

For adsorbant, see section 2.

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 (chlorobutyl) with attached needle and needle-shield (polyisoprene).

0.5 ml of suspension in pre-filled syringe (type I glass) with a plunger-stopper (chlorobutyl), without needle.

0.5 ml of suspension in pre-filled syringe (type I glass) with a plunger-stopper (chlorobutyl), with 2 separate needles.

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 pre-filled 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

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

YYYY-MM-DD