For the use only of registered medical practitioners or a hospital or a laboratory

Inactivated Hepatitis A Vaccine Adsorbed I.P.

AVAXIM 80 U Pediatric

Suspension for injection in prefilled syringe

1. Name of the Medicinal Product

Inactivated Hepatitis A Vaccine adsorbed I.P.
AVAXIM 80 U Pediatric, Suspension for injection in prefilled syringe

2. Qualitative and quantitative composition

Hepatitis A virus GBM strain* (inactivated) **…….80 U***
For one dose of 0.5 mL.
Per container (for one 0.5 ml dose)

Component[1]	**Quantity (per container)**	**Function**
Hepatitis A virus, GBM strain (inactivated)	80 U	Active substance
Aluminium hydroxide, hydrated	0.15 milligrams Al^{3+}	Adjuvant
Phenoxyethanol – Ethanol (50% v/v solution) - 2-phenoxyethanol - ethanol anhydrous	 2.5 µL 2.5 µL	Preservative
Formaldehyde	12.5 µg	Preservative
1 x C Medium 199 Hanks (without phenol red)[2]	q.s. 0.5 mL	Stabilizer and buffer

* Cultured on MRC-5 human diploid cells.
** Adsorbed on hydrated aluminium hydroxide (0.15 milligrams of Al).
*** In the absence of an international standardised reference, the antigen content is expressed using an in-house reference
[1] – Hydrochloric acid and or sodium hydroxide can be used for pH adjustment. These components are only present in trace amount.
[2] - 1 x C Medium 199 Hanks (without phenol red) is a complex mixture of amino acids (including phenylalanine), mineral salts, vitamins and other substances (see detailed composition in section 6.1). It is supplemented with polysorbate 80 and is reconstituted in water for injections.

3. Pharmaceutical form official

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 a vaccine. Vaccines are used to protect you against infectious diseases.

This vaccine helps protect your child aged from 12 months to 15 years inclusive against the infection caused by the hepatitis A virus.

Hepatitis A infection is caused by a virus which attacks the liver.

It can be transmitted by food or beverages containing the virus. Symptoms include yellowing of the skin (jaundice) and feeling generally unwell.

When your child receives an injection of AVAXIM 80 U PEDIATRIC, the natural defences of his/her body develop a protection against the infection caused by the hepatitis A virus.

This vaccine should be administered in accordance with official recommendations.

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 and /or routes of administration

AVAXIM 80 U PEDIATRIC must be administered into a muscle (in order to minimise local reactions), in the outer upper part of your child's arm.

If your child has haemophilia or if he/she bruises or bleeds easily, the vaccine can exceptionally be administered under his/her skin.

This vaccine must never be administered into a blood vessel.

The doctor must not inject the vaccine into the skin.

The vaccine will not be administered into the buttock.

The doctor will shake the syringe immediately before the injection and will make sure the liquid is turbid and whitish and there are no foreign particles.

In case you forgot to take Avaxim 80U Pediatric:

Your doctor will decide when to administer this missing dose.

If you have any further questions on the use of this medicine, ask your doctor.

4.3 Contraindications

- If your child is allergic to the active substance or any of the other ingredients of AVAXIM 80 U PEDIATRIC (listed in section 2 and 6.1)
- If your child is allergic to neomycin (an antibiotic used during the manufacturing process of the vaccine, and which may be present in it in small amounts).
- If your child is allergic to AVAXIM 80 U PEDIATRIC.
- If your child has a disease with a high temperature. Vaccination should be postponed until he/she has recovered.

4.4 Special warnings and precautions for use

- If your child has a weakened immune system due to:
    - Corticosteroids, cytotoxic drugs, radiotherapy or other treatments likely to weaken his/her immune system. Your doctor may wait until treatment is over.
    - HIV (Human immunodeficiency virus) infection or any other diseases that weaken his/her immune system. Vaccine administration is recommended although it may not protect him/her as well as it protects people with a normal immune system.
- If your child has a liver disease.
- If your child has haemophilia or is easily subject to bruises or bleeding.
- Fainting can occur (especially in adolescents) following, or even before, any needle injection. Therefore, tell your doctor or nurse if your child fainted with a previous injection.

This vaccine will not protect your child against other viruses that infect the liver (such as hepatitis B, hepatitis C or hepatitis E viruses).
If your child is already infected by the hepatitis A virus at the time of the administration of AVAXIM 80 U PEDIATRIC, the vaccination may not work properly.
The vaccine cannot cause the infections against which it protects.
As with all vaccines, not all people who receive AVAXIM 80 U PEDIATRIC will definitely be protected against hepatitis A.

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 immunological response may be diminished in case of immunosuppressive treatment.

The vaccine may be administered at the same time as at two different injection sites, with the routine booster vaccines given to children during the second year of life, i.e. the various vaccines against diphtheria, tetanus, pertussis (acellular or whole cell), *haemophilus influenzae* type b and inactivated or oral poliomyelitis.

This vaccine can also be administered at the same time as a vaccine against measles, mumps and rubella.

All injections must be perfomed in separate injection sites, i.e. in another part of the body such as another arm or another leg, and the vaccines must not be mixed in the same syringe.

This vaccine can be administered at the same time as immunoglobulins (antibodies obtained from blood donation) but in two separate injection sites.

AVAXIM 80 U PEDIATRIC may not work so well if it is given at the same time as the immunoglobulins. However, your child will probably be protected against the hepatitis A infection.

This vaccine can be used as a booster dose in subjects who have received a first vaccination with another inactivated hepatitis A vaccine. If your child is taking or has recently taken any other medicines, even one obtained without a prescription, please tell your doctor.

4.6 Fertility, Pregnancy and lactation

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

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

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before receiving this vaccine.

Ask your doctor advice before using any medicinal product.

4.7 Effects on ability to drive and use machines

The vaccine is unlikely to have any effects on the ability to drive and use machines. However, no studies on this were performed.

4.8 Undesirable effects

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

Very common: ≥ 1/10 (≥ 10%)

Common: ≥ 1/100, <1/10 (≥ 1% and < 10%)

Uncommon: ≥ 1/1000, <1/100 (≥ 0.1% and < 1%)

Rare: ≥1/10 000, <1/1000 (≥ 0.01% and < 0.1%)

Very rare: <1/10 000 (< 0.01%)

Not known (cannot be estimated from the available data).

Adverse event data are derived from clinical studies and worldwide post-marketing experience.

- **Data from clinical studies**

More than 6,200 children aged 12 months to 15 years were vaccinated with "Trade Name" during clinical trials.

A pooled analysis has been performed integrating data from 5458 subjects included in 15 clinical trials conducted between 1996 and 2014.

The table below summarizes the percentage of subjects from this pooled analysis experiencing at least one solicited adverse reaction within 7 days post vaccination.

For each reaction, the frequency has been defined by the number of subjects experiencing the reaction divided by the number of subjects with available data.

Subjects experiencing at least one:	*After the first dose (N=5458)*	*After the second dose (N=4777)*	**After any dose** *(N=5458)*
Adverse Reaction			
General disorders and administration site condition			
Injection site Pain	*13.4%- Very common*	*9.8% - Common*	*18.1%* - **Very common**
Injection site erythema	*4.6%- Common*	*2.3% - Common*	*6.3%* - **Common**
Injection site Induration/Oedema	*2.5%- Common*	*1.3% - Common*	*3.3%* - **Common**
Injection site haematoma	*1.5%- Common*	*0.7% - Uncommon*	*2.1%*- **Common**
Malaise	*8.9% Common*	*6.3% - Common*	*13.6%* - **Very common**
Pyrexia	*5.5% - Common*	*2.4% - Common*	*7.2%*- **Common**
Asthenia/Drowsiness	*4.5% - Common*	*1.4% - Common*	*5.5%*- **Common**
Metabolism and nutrition disorders			
Decreased appetite	*6.1%- Common*	*2.2% -Common*	*7.7%*- **Common**
Psychiatric disorders			
Irritability	*5.1%- Common*	*1.4% - Common*	*6.1%*- **Common**
Insomnia	*1.7% - Common*	*1.0% - Common*	*2.5%*- **Common**
Crying abnormal	*13.0% - Very common*	*0.9%- Uncommon*	*13.1%*-**Very common**
Nervous system disorders			
Headache	*8.6% - Common*	*4.6% - Common*	*11.5%*- **Very common**
Gastrointestinal disorders			

Subjects experiencing at least one:	*After the first dose (N=5458)*	*After the second dose (N=4777)*	**After any dose** *(N=5458)*
Adverse Reaction			
Abdominal pain	*4.6% - Common*	*2.4%- Common*	*6.6%* - **Common**
Vomiting	*3.5% - Common*	*1.4% - Common*	*4.7%*- **Common**
Diarrhea	*3.6% - Common*	*1.6% - Common*	*4.9% –* **Common**
Nausea	*3.0% - Common*	*1.0% - Common*	*3.9%* - **Common**
Skin and subcutaneous tissue disorders			
Rash	*0.0%*	*0.5% - Uncommon*	*0.5%*- **Uncommon**
Urticaria	*0.9%- Uncommon*	*0.0%*	*0.9%*- **Uncommon**
Musculoskeletal and connective tissue disorders			
Arthralgia	*1.8%- Common*	*0.8% - Uncommon*	*2.5%* - **Common**
Myalgia	*6.7% - Common*	*4.7% - Common*	*9.6%* - **Common**

Most adverse reactions were confined to the first few days following vaccination with spontaneous recovery. The incidence of severe (grade 3) reactions was low. Furthermore, reactions were less frequently reported after the booster dose than after the first dose.

In subjects seropositive against hepatitis A virus, Avaxim 80 U Pediatric was as well tolerated as in seronegative subjects.

- **Data from Post-marketing experience**

Based on spontaneous reporting, the following additional adverse event has been reported during the commercial use of Avaxim 80 U Pediatric. This event has been very rarely (< 0.01%) reported; however as exact incidence rates cannot be calculated precisely, its frequency is qualified as "Not known".

Nervous system disorders

- **Vasovagal syncope**

4.9 Overdose

An overdose is unlikely to provoke any harmful effects.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Avaxim 80 U Pediatric is prepared from hepatitis A virus grown, harvested, purified and formaldehyde inactivated. Avaxim 80 U Pediatric confers immunity against hepatitis A virus by inducing antibody (anti-HAV) titers longer lasting and higher than those obtained after passive immunization with immunoglobulins. Avaxim 80 U Pediatric has been demonstrated to elicit

protective anti-HAV titers (titre ≥20 mIU/ml) within 2 weeks in over 95% of individuals and in 100% before the booster dose administered 6 months after the first dose.
Anti-HAV titers are reinforced after a booster dose.
A study conducted in Argentina provided long term persistence antibody data on 2 groups, one who received a single dose and another one who received the standard 2 doses schedule. It was shown 7 years after vaccination that the group who received a single dose showed similar seroprotective level than the one who received 2 doses.
Data relative to long-term persistence of anti-HAV antibodies following booster vaccination with Avaxim 80 U Pediatric indicate that anti-HAV antibodies persist up to 14-15 years in healthy individuals.
Mathematical calculations using data available after 14-15 years following 2 doses of Avaxim 80 U Pediatric administered 6 months apart in an intermediate endemic setting, predict persistence of protective anti-HAV antibody titers in over 88% of individuals for at least 20 to 30 years.

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

Keep out of the reach and sight of children.

The product should be stored at 2°C - 8°C (in a refrigerator) and protected from light.

Do not freeze. Do not use after the expiry date indicated on the label or on the box.

The expiry date refers to the last day of that month.

The vaccine should not be used in case of discolouration or presence foreign particles.

Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6.5 Nature and contents of container

Avaxim 80U Pediatric is a suspension for injection in pre-filled syringe(0.5mL) with or without needle-box of 1,10 or 20.
All pack sizes may not be marketed.
The hepatitis A vaccine (inactivated, adsorbed) is a turbid and whitish suspension.

The following information is intended for health care professionals only:

The vaccine must not be mixed with other vaccines in the same syringe.

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.

7. MANUFACTURED BY:

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