Unit: Technical Assessment Unit

Public assessment report for biological products

(Avaxim 80 pediatric)

Administrative information:

Trade name of the medicinal product:	Avaxim 80 pediatric
INN (or common name) of the active substance(s):	Inactivated Hepatitis A vaccine
Manufacturer of the finished product	Sanofi Pasteur Parc Industriel d'Incarville, 27100, Val de Reuil France
Marketing Authorization holder	Sanofi Pasteur
Applied Indication(s):	active immunization against infection caused by HAV in children aged from 12 months of age to 15 years inclusive.
Pharmaceutical form(s) and strength(s):	pre-filled syringe
Route of administration	IM
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

HAV	Hepatitis A Virus
WHO	World Health Organization
BSA	Bovine Serum Albumin
MA	Marketing authorization
BCA	Bicinchoninic Acid
AgU	Antigen unit
Ph. Eur	European Pharmacopoeia
TRS	Technical Report Series
AE	Adverse Event
AgU	Antigen unit
CI	Confidence Interval
GMT	Geometric Mean Titres
HD	Human dose
IU	International Unit
LLOQ	Lower Limit of Quantification
MMR	measles, mumps, and rubella
mIU/ml	milli-International Units per milliliter

mL	milliliter
SAE	Serious Adverse Event
SC	Seroconversion Rate

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1. **General introduction about the product including brief description of the AI, its mode of action and indications:**
   The Sanofi Pasteur Inactivated Hepatitis A vaccine is prepared from cultured, purified and formaldehyde-inactivated hepatitis A virus. The HAV strain used in the vaccine was isolated in 1975 from a human case during an outbreak in Gomaringen (Germany) by B.Flehmig at Tübingen University.
   The viral strain was adapted and propagated on a primary human kidney cell culture followed by an adaptation in diploid human fibroblast cells and MRC-5 cells.
2. **Quality aspects:**

2.2.1 Introduction

As mentioned in the aforementioned section.

2.2.2 Drug Substance (Active ingredient):

- **General information**
  The immunochemical properties of the inactivated adsorbed harvest allow the vaccine to induce an active immunization against Hepatitis A virus infection. The impurities tested for and related to the reagents used during the process developed for manufacture of the drug substance have been extensively studied and discussed in the MA file.
- **Manufacture, process controls and characterization:**
  Manufacturer:
  The drug substance is manufactured and controlled at the following site:
  Name(s) Sanofi Pasteur
  Address Campus Mérieux
  1541, avenue Marcel Mérieux
  69280 Marcy l'Etoile - France
- **Description of Manufacturing Process and Process Controls**
  The Working Virus Seed Lot is inoculated into MRC-5 cells which have been amplified to the suitable level to enable virus propagation. The virus is then harvested after sonication of the cells as a single harvest. The single harvest is filtered and then purified.
- **Control of Materials.**
  The list of materials used in the manufacture of the inactivated Hepatitis A drug substance and tested according to Pharmacopoeia monographs and in-house specifications are provided in the MA file.
- **Controls of Critical Steps and Intermediates**
  In-process controls and Quality control tests performed on the intermediate produced during the manufacture of the Drug Substance Control cells, Single harvest, clarified harvest, intermediate of purification, and Purified harvest are discussed in the MA file.

Quality control test performed on the intermediate as are performed.

- **Process Validation**
  All the important steps and procedures in the manufacturing have been validated.
  The results showed that the manufacturing process is consistent.
- **Manufacturing Process Development**
  The Inactivated Hepatitis A manufacturing process has remained constant and has continually produced a highly immunogenic Hepatitis A antigen.

- **Specification**
  Specifications of Inactivated Hepatitis A Harvest is provided in MA file.
- **Analytical Procedures**
  Analytical Procedures are included in details in the dossier including summaries of test principle, equipment, reagents, acceptance and validity criteria.
- **Reference Standards or Materials**
  The reference standards or materials used for the Hepatitis A drug substance and certificates of analysis are provided in the MA file.
- **Container closure system**
  The inactivated Hepatitis A Harvest (Drug Substance) is stored in sterile polypropylene vials with polypropylene stoppers.
- **Stability of drug substance**
  Storage condition: 2-8 °C for 6 months in polypropylene vials.

2.2.3 Drug product:

- **Description of manufacturing process and process controls along with manufacturers and responsibilities**
  Manufacturer: Sanofi Pasteur 1541, avenue Marcel Mérieux 69280 Marcy l'Etoile,France
  Sanofi Pasteur Parc Industriel d'Incarville, 27100, Val de Reuil France
- **Control of critical steps and intermediates**

Summary of the controls in place to monitor the critical steps are provided in the MA file.

- **Process validation and / or evaluation**

The process validation covering the manufacturing steps and parameters studied for Hepatitis A Pediatric Vaccine are listed in the MA file.

- **Product specification:**

-The specifications of Hepatitis A Pediatric Vaccine Final Bulk Product and Filled Product take into account the requirements laid down in:
Ph. Eur. Monograph No. 1107 "Hepatitis A Vaccine (inactivated, adsorbed)", current edition; Ph. Eur. Monograph No. 0153 "Vaccines for human use", current edition; Ph. Eur. Monograph No. 0520 "Parenteral preparations", current edition;
The recommendations of WHO Technical Report Series (TRS) No. 858 Annex 2 (1995)
"Requirements for Hepatitis A Vaccine (inactivated)".
-The release specifications for Hepatitis A Pediatric Vaccine FBP and Filled Product are
summarized in the MA file.

- **Characterization of impurities.**

Pharmacopoeial grade excipients and non-pharmacopoeial grade excipient contained in the Hepatitis A Pediatric Vaccine are listed in MA file.
No novel excipient is used in the manufacture of Hepatitis A Pediatric Vaccine.

- **Reference Standards or Materials.**

The reference standard used to determine the content of Hepatitis A antigen in the vaccine, with the Ph. Eur. 2.7.14 in vitro method, at the Filled Product Stage, is an in-house batch of Inactivated Hepatitis A Harvest (Drug Substance).
It is calibrated against the current international reference standard.

- **Container closure system**

The Hepatitis A Pediatric Vaccine Final Bulk Product is stored in sterile stainless-steel tanks prior to filling.
The container closure systems consist of:
• A single dose type I glass syringe with attached stainless steel needle containing a bromochlorobutyl, chlorobutyl, or bromobutyl plunger stopper and a polyisoprene needle shield.
• A single dose type I glass syringe without attached needle containing a bromochlorobutyl, chlorobutyl, or bromobutyl plunger stopper and a bromochlorobutyl or synthetic isoprene- bromobutyl tip-cap.

- **Stability of the drug product.**

-Based on available stability data,
approved Shelf Life: 36 months
approved Storage Conditions: 2-8 ºC
DO NOT FREEZE. Discard if frozen. • Store protected from light

3. Non–clinical aspect:

Avaxim is a purified and formaldehyde-inactivated hepatitis A virus obtained from GBM strain cultured on MRC-5 human diploid cells. Each human dose contains 160 antigen units. The pharmaceutical form of this vaccine is a suspension for injection by the intramuscular route. Immunity appears shortly after the first injection and more than 90 % of immunocompetent

subjects are protected (titre above 20 mlU/ml) 14 days after vaccination. One month after first injection, 100 % of subjects are protected. Immunity persists for at least six months and is reinforced after a first booster dose. Antibody titres obtained after the first booster are consistent with a projected 10-year protection.

Pharmacology: Immunogenicity of an experimental vaccine batch derived from GBM strain was evaluated on mice, monkeys and guinea pigs. Studies carried out on various animal species showed comparable immune response to the vaccine when compared with the "reference vaccine".

Pharmacokinetics: Specific non-clinical studies on absorption, distribution, metabolism, excretion, or drug interactions were not applicable according to WHO guidelines on nonclinical evaluation of vaccines Annex 1 (TRS, No. 927, 2005).

Toxicology: Single and repeated dose toxicity studies were conducted in mice and rats. In addition, a local tolerance study in rabbits and a hypersensitivity assessment in guinea pigs were submitted. The results from the toxicological studies carried out on various animal species demonstrate that the Hepatitis A vaccine presents a wide margin of safety after single and repeated administration of doses up to 2 HD (640 AgU), and does not cause a hypersensitivity reaction differing from that usually observed with this type of product.
The local tolerance is acceptable considering the immunological nature of the product, its composition and finally the production process.

4. **Clinical aspect:**

Sanofi Pasteur developed a pediatric inactivated hepatitis A vaccine (adsorbed) containing the GBM strain of the hepatitis A virus. The clinical program comprised 14 studies:

- Phase II: 3 studies
- Phase III: 9 studies
- Phase IV: 2 studies

Across all phases, the studies consistently evaluated the safety, efficacy, and immunogenicity of the vaccine in pediatric populations aged 12 months to 15 years.

➢ **<u>Clinical Efficacy and Immunogenicity</u>**

- Following the **first injection**, more than **99%** of subjects developed detectable anti-HAV antibodies (≥ LLOQ) within two weeks.

- In pooled analyses, **≥ 98%** of subjects achieved antibody levels ≥ 20 mIU/mL after the first dose, with **100% seroprotection** observed prior to booster administration in nearly all studies.
- Post-booster, **virtually all participants (≥ 99.8%)** maintained anti-HAV titers ≥ 20 mIU/mL, with **geometric mean titers (GMTs)** ranging from **3,100 to > 9,000 mIU/mL**, confirming a strong **anamnestic response**.
- Subjects with pre-existing low-level antibodies at baseline achieved **higher GMTs** post-vaccination compared to seronegative participants.
- Geographical analysis indicated slightly higher responses after the first dose in regions of **high or intermediate endemicity**, while booster responses were comparable across all regions.
- **Concomitant administration** with pediatric vaccines (DTwP//Hib + OPV, DTacP-IPV//Hib, or MMR) showed **no negative impact** on immune responses.
- **Long-term persistence** of seroprotection was demonstrated:
    - **Up to 3 years** post-booster in low-endemicity regions (e.g., Israel, Study HAF11).
    - **Up to 10 years** post-vaccination in intermediate-endemicity regions (e.g., Argentina, Study HAF82), with evidence of sustained protection following a single dose, likely enhanced by natural HAV exposure.
- The vaccine can be used to **complete vaccination series** initiated with other pediatric hepatitis A vaccines.

➢ **Clinical Safety**

- The most frequent **injection-site reactions** were **pain/tenderness**, reported in:
    - 33.4% (12–15 years), 17.4% (≤ 23 months), and 14.7% (2–11 years).
    - **Erythema/redness** was more common in infants ≤ 23 months (9.9%) than older children (1.1%).
- The most common **systemic reactions**:
    - ≤ 23 months: appetite loss (14.2%), irritability (13.7%), crying (13.1%)

- 2–11 years: malaise (11.3%), headache (8.7%), myalgia (7.0%)
- 12–15 years: malaise (19.8%), headache (19.8%), myalgia (16.8%)

- **Serious adverse events (SAEs)** were rare:

  2.1% (≤ 23 months), 1.2% (2–11 years), 0.5% (12–15 years), mostly due to infections (e.g., pneumonia, gastroenteritis).

- No **vaccine-related deaths** occurred. Only **two vaccine-related SAEs** (diarrhea; arthralgia/vasculitis) were reported during clinical development.
- **Safety was consistent** across genders and between groups receiving the vaccine alone or co-administered with other routine pediatric vaccines.
- Co-administration with **MMR** showed a mild, non-clinically significant increase in minor reactions.
- Overall, the **safety profile** was comparable to that of other licensed inactivated hepatitis A vaccines, with most adverse events being **mild, transient, and self-limiting**.

➢ **Benefit–Risk Assessment**

- A **two-dose schedule** (≥ 6 months apart) provided rapid and robust protection:
  - 95% seroprotection within **14 days** after the first dose.
  - 100% protection within **28 days** post-booster (anti-HAV ≥ 20 mIU/mL).
- Protection was **independent of age**, prior HAV exposure, or endemicity level.
- **Long-term protection** demonstrated for **≥ 10 years**, with modeling suggesting persistence for **20–30 years**, potentially **lifelong** in high-endemic regions.
- The vaccine was **well tolerated**, with **no new safety signals** identified.
- When co-administered with routine pediatric vaccines (DTwP/Hib, IPV, MMR), there was **no impact** on immunogenicity or safety.

➢ **Overall Conclusion**

The Sanofi Pasteur Pediatric Hepatitis A Vaccine (Avaxim 80), administered as a two-dose series (first dose followed by a booster between 6 and 36 months, and up to 7 years later),

demonstrates an excellent immunogenicity profile, favorable safety, and durable protection against hepatitis A infection in children aged 12 months to 15 years.

The overall benefit–risk profile is clearly favorable, supporting its continued use in pediatric immunization programs globally.

5. General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved.