AVAXIM 80 U PEDIATRIQUE, suspension for injection in prefilled syringe, inactivated, adsorbed hepatitis A vaccine
Box of 1 glass prefilled syringe with needle containing 0.5 ml (CIP: 356 772-4)

AVAXIM 80 U PEDIATRIQUE, suspension for injection in prefilled syringe, inactivated, adsorbed hepatitis A vaccine
Box of 1 glass prefilled syringe without needle containing 0.5 ml (CIP: 356 777-6)

Applicant: SANOFI PASTEUR MSD

Hepatitis A virus (strain GBM*) inactivated **.................................80 U***
* Cultured on MRC-5 human diploid cells
** Adsorbed on aluminium hydroxide (amount equivalent to 0.15 mg of aluminium)
*** Antigen units, measured according to the manufacturer’s in-house method.

ATC code: J07BC02

Date of first Marketing Authorisation: 04/07/2001, revision 04/12/2003

Reason for request: Inclusion in the list of medicines reimbursed by National Health Insurance and approved for hospital and various public services use in the populations recommended by the French High Council of Public Health (Haut Conseil de la Santé Publique).

Additional document: 2010 vaccination schedule and recommendations from the French High Council of Public Health

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Inactivated, adsorbed hepatitis A virus

1.2. Indication
“AVAXIM 80 U PEDIATRIQUE 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 particular 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 faeco-oral routes.
The possibility of transmission through the blood or by sexual contacts (oral-anal relations) has also been proved.”

1.3. Dosage (see SmPC)
“Primary vaccination is achieved with one single dose of vaccine. The recommended dosage is 0.5 ml for each injection. In order to provide long term protection, a booster dose is recommended 6 to 18 months after the initial dose.
HAV antibody persistence following vaccination is not currently available. Available data suggest that HAV antibodies persist at protective levels up to ten years after primary vaccination.”

2. SIMILAR MEDICINAL PRODUCTS

2.1 ATC Classification
J Antiinfectives for systemic use
J07 Vaccines
J07B Viral vaccines
J07BC Hepatitis vaccines
J07BC02 Hepatitis A, inactivated, whole virus

2.2 Medicines in the same therapeutic category
HAVRIX NOURRISONS ET ENFANTS 720 U/0.5 ml, suspension for injection, single dose.
Inactivated, adsorbed hepatitis A vaccine: approved for hospital and various public services use, not reimbursed by National Health Insurance.
VAQTA 25 U/0.5 ml, purified, inactivated hepatitis A vaccine: approved for use by hospitals and various public services, not reimbursed by National Health Insurance.

2.3 Medicines with a similar therapeutic aim (bivalent vaccine)
TWINRIX ENFANT, suspension for injection. Vaccine against hepatitis A (inactivated) and hepatitis B (ADNr) (HAB) (adsorbed): approved for hospital and various public services use, not reimbursed by National Health Insurance.
3. UPDATE OF AVAILABLE DATA

The dossier submitted by the company comprises in particular the results of three published studies that evaluated the immunogenicity of AVAXIM 80 U PEDIATRIQUE in healthy children:
- two non-comparative phase III studies: study by Dagan et al., 1999; study by Lopez et al., 2001
- a phase III study that evaluated the immunogenicity, safety and interchangeability of AVAXIM 80 U PEDIATRIQUE and HAVRIX 720: study by Abarca et al., 2008

The application submitted by Sanofi Pasteur MSD for inclusion in the list of medicines reimbursed by National Health Insurance and for approval for use in hospitals and various public services concerns the following populations as defined in the 2010 vaccination schedule recommendations:
- young people living in care homes and institutions for handicapped children and youth,
- patients with cystic fibrosis and/or chronic hepatobiliary pathologies likely to develop into chronic liver disease (in particular due to hepatitis B or C),
- children aged 1 year and upwards with family members originally from a country where the disease is highly endemic and who may be likely to visit that country,
- vaccination following a case of hepatitis A in the family and in communities living in conditions of poor hygiene.

3.1 Immunogenicity data for the general population (excerpt from the SmPC)

“This vaccine confers immunity against the hepatitis A virus by inducing antibody titres longer lasting and higher than those obtained after passive immunisation with immunoglobulins. This vaccine has been demonstrated to elicit protective antibody titres against hepatitis A virus (≥ 20 mIU/ml) within 2 weeks following the injection in over 95% of individuals and in 100% of individuals before the booster dose. Immunity persists for 6 to 18 months and is reinforced by a booster dose. Long-term persistence of antibodies to hepatitis A virus after a booster dose is under evaluation. However, antibody titres after the first booster are consistent with long-term protection (at least 10 years).”

3.2 Immunogenicity studies submitted by the company

The dossier submitted by the company comprises in particular the results of three published studies that evaluated the immunogenicity of AVAXIM 80 U PEDIATRIQUE in healthy children:
- two non-comparative phase III studies: study by Dagan et al., 1999; study by Lopez et al., 2001
- a phase III study that evaluated the immunogenicity, safety and interchangeability of AVAXIM 80 U PEDIATRIQUE and HAVRIX 720: study by Abarca et al., 2008

---

Study by Dagan et al., 1999

Main objective: To evaluate the immunogenicity of the vaccine AVAXIM 80 U PEDIATRIQUE in healthy children.

Methodology: Open study carried out in Israel in 189 children aged from 18 months to 15 years vaccinated with AVAXIM 80 U PEDIATRIQUE according to a 0-6 months schedule. The GMT (geometric mean titre) and hepatitis A vaccine (HAV) antibody titre were measured at weeks 2, 24, 28 and 76 after primary vaccination. Subjects with an HAV antibody titre ≥ 20 mIU/ml were considered seropositive for HAV.

Results: The rate of seroconversion was 95.4% two weeks after the first dose and 100% in all age groups just before the booster dose. 76 weeks (19 months) after primary vaccination, a seroprotective HAV antibody titre had persisted in all children and the GMT was 797 mIU/ml (95% confidence interval (CI): 702 to 905 mIU/ml).

3-year follow-up (Dagan R. et al., 2005)5

A seroprotective HAV antibody titre had persisted in all children followed up 1 year, 2 years and 3 years after the first dose of AVAXIM 80 U PEDIATRIQUE (177 children followed up after 1 year; 149 children followed up after 2 years; 135 children followed up after 3 years).

Study by Lopez et al., 2001

Main objective: To evaluate the safety and immunogenicity of AVAXIM 80 U PEDIATRIQUE in healthy children.

Methodology: Open study carried out in Argentina in 537 children aged from 1 to 15 years vaccinated with AVAXIM 80 U PEDIATRIQUE according to a 0-6 months schedule. The immunogenicity of the vaccine was evaluated in the subgroup of 120 first children aged from 1 to 4 years included in the study. The GMT and the HAV antibody titre were measured at weeks 0, 2, 24 and 27. Subjects with an HAV antibody titre ≥ 20 mIU/ml were considered seropositive for HAV.

Results: In the 111 children aged from 1 to 4 years initially seronegative for HAV, the seroconversion rate was greater than 99% two weeks after the first injection of vaccine and the GMT was 98.5 mIU/ml. The booster dose after 6 months increased the HAV antibody titre by a factor of 35.

Study by Abarca et al., 2008

Main objective: To evaluate the immunogenicity, safety and interchangeability of the vaccines AVAXIM 80 U PEDIATRIQUE and HAVRIX 720 U in children.

Methodology: Randomised study carried out in 332 children aged from 1 to 15 years who received either:
- 2 doses of AVAXIM 80 U PEDIATRIQUE,
- 2 doses of HAVRIX 720 U, or
- 1 dose of HAVRIX 720 U followed by a dose of AVAXIM 80 U PEDIATRIQUE.

The two doses were administered 6 months apart.

The rate of seroconversion (percentage of children with an HAV antibody titre ≥ 20 mIU/ml) was evaluated 14 days after the first dose of vaccine, then before and 1 month after the second dose.

Results:
- 14 days after primary vaccination, the seroconversion rates were 99.4% for AVAXIM 80 U PEDIATRIQUE and 100% for HAVRIX 720 (95% CI of the difference between the seroconversion rates of the two vaccines: -4.3; 2.1) The GMTs were 311 mIU/ml (95% CI: 274 to 353) for AVAXIM 80 U PEDIATRIQUE and 138 mIU/ml (95% CI: 120 to 159) for HAVRIX 720.
- One month after the second dose, the seroconversion rate was 100% in the three groups.

The GMTs were:
- for the AVAXIM 80/AVAXIM 80 group: 8537 mIU/ml (95% CI: 7768 to 9382),
- for the HAVRIX 720/HAVRIX 720 group: 4008 mIU/ml (95% CI: 3261 to 4926)
- for the HAVRIX 720/AVAXIM 80 group: 7144 mIU/ml (95% CI: 5907 to 8640).

3.3 Adverse effects (excerpt from SmPC)
"More than 3000 children aged from 12 months to 15 years (around 5900 administered doses) were vaccinated with this vaccine during clinical development.
All adverse reactions were moderate and confined to the first few days following vaccination with spontaneous recovery. Reactions were less frequently reported after the booster dose than after the first dose.
However, as with all medicines, expanded commercial use of the vaccine might reveal rarer adverse effects.
The most common reactions with an incidence of 1% to 10% are local reactions at the injection site such as pain, redness, oedema or induration and systemic reactions such as headache, gastrointestinal tract disorders (abdominal pain, diarrhoea, nausea, vomiting), myalgia or arthralgia, transitory behaviour changes (appetite decrease, insomnia, irritability), fever, asthenia.
The less common reactions with an incidence of less than 1% are cutaneous manifestations (rash, urticaria)."

3.4 Conclusion
AVAXIM 80 U PEDIATRIQUE has been demonstrated to elicit protective antibody titres against hepatitis A virus (≥ 20 mIU/ml) within 2 weeks following the injection in over 95% of individuals and in 100% of individuals before the booster dose.
The standard immunisation schedule is one dose followed by a booster dose to be given preferably 6 to 18 months after the first injection.
"HAV antibody persistence following vaccination is not currently available. Available data suggest that HAV antibodies persist at protective levels up to ten years after primary vaccination."

No clinical data was provided in specific populations.

There have been no studies of the protective efficacy of AVAXIM 80 U PEDIATRIQUE. This vaccine is well tolerated.
4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1 Actual benefit

Hepatitis A is a usually mild disease, but can however give rise to serious forms (sometimes fatal, mainly in patients with chronic liver disease). Vaccination aside, the basis for prevention is the improvement of personal and collective hygiene.

The vaccine is a preventive therapy.

The efficacy (immunogenicity)/adverse effects ratio for this medicinal product is high.

There is no other vaccine alternative reimbursed by National Health Insurance.

Public health benefit

Although normally a mild condition, particularly in children, hepatitis A can evolve in rare cases into severe forms (fulminant hepatitis), particularly in patients with chronic underlying liver disease. In France, 1204 cases were reported in 2008 through the notifiable illness system, of which 45% necessitated hospitalisation. According to the database of the medical causes of deaths, the number of deaths due to hepatitis A in France was 3 in 2006 and 2 in 2007. The public health burden of hepatitis A is therefore low.

Taking into account the steady increase in the susceptibility of the French population to the hepatitis A virus and the potential risk of hepatitis A-related decompensation in patients with chronic liver disease, the prevention of hepatitis A is an identified public health need (Guidelines of the French High Council of Public Health, Public Health Law 2004).

The efficacy of the vaccine AVAXIM was established solely on the basis of immunogenicity studies carried out in healthy subjects.

In the absence of data allowing us to estimate the proportion of decompensation cases induced by hepatitis A in patients with chronic liver disease, the impact of vaccination with AVAXIM in terms of complications or deaths avoided in these populations is hard to quantify.

According to notifiable illness data, the principal risk factors are residence outside metropolitan France (reported in 40% of cases) and the presence of persons infected with hepatitis A in the patient’s family (reported in 50% of cases). The indirect impact of the vaccine AVAXIM on the spread of an outbreak may be only low, given the number of clusters observed in France (about 400 cases in 2008). However, in the absence of available clinical study data this impact has not been clearly established, particularly where there are only limited outbreaks such as in France. Moreover, there have been no comparative studies versus the implementation of preventive hygiene and dietary measures.

It is therefore uncertain whether the results of the studies can be carried over into clinical practice; this may depend on the achievement of adequate vaccination coverage in the populations targeted by the recommendations.

The potential impact of the vaccine AVAXIM on the public health system cannot be estimated.

7 Statistics on the medical causes of deaths, CépiDc at INSERM [National Institute of Health and Medical Research]. CépiDc: http://www.cepidc.vesinet.inserm.fr/
The medicinal product AVAXIM should contribute to meet an identified public health need. However, based on the current level of knowledge, the expected benefit to public health of AVAXIM in the populations recommended by the French High Council of Public Health is hard to quantify.

The actual benefit of AVAXIM is substantial in patients with cystic fibrosis and patients with active chronic liver disease.

4.2 Improvement in actual benefit (IAB)

The Committee stresses that hepatitis A is a usually mild disease, but can give rise to serious forms that in exceptional cases can be fatal in patients with progressive chronic liver disease. It does, however, regret the absence of recent clinical data and data from comparative studies versus the implementation of preventive hygiene measures.

AVAXIM 80 U PEDIATRIQUE offers a moderate improvement in actual benefit (IAB level III) in terms of immunogenicity and safety in the preventive treatment of a population limited to patients with cystic fibrosis and patients with active chronic liver disease.

4.3 Therapeutic use

The Transparency Committee points out that the French High Council of Public Health considers generalised vaccination against hepatitis A in France could be disproportionate given the low incidence of the disease.

4.3.1 Recommendations listed in the 2010 immunisation schedule guidelines from the French High Council of Public Health (children):

According to the 2010 vaccination schedule recommendations⁸, preventive vaccination against hepatitis A is recommended in children in the following populations:
- young people living in care homes and institutions for handicapped children and youth,
- patients with cystic fibrosis and/or chronic hepatobiliary pathologies likely to develop into chronic liver disease (in particular due to hepatitis B or C),
- children aged 1 year and upwards with family members from a country where the disease is highly endemic and who may be likely to visit that country,
- recommendations on vaccination following a case of hepatitis A:
  - in the immediate family
  - in communities living in conditions of poor hygiene.

---

4.3.2 Therapeutic use of the vaccine AVAXIM in the prevention of hepatitis A in children in the context of reimbursement by National Health Insurance

The Transparency Committee considers that reimbursement by National Health Insurance of the vaccine AVAXIM 80 U PEDIATRIQUE is justified in patients with cystic fibrosis and patients with active chronic liver disease, in particular due to hepatitis B or C, for whom hepatitis A could develop into serious forms that can be fatal in exceptional cases.

Moreover, it notes that:
- resorting to vaccination in the event of an outbreak in schools or in institutions for people with psychomotor handicap is a decision that must be taken by the regional or national authorities following a survey identifying conditions of poor hygiene in which lasting improvement is difficult to achieve in certain communities.

- unimmunised children born in France to immigrant parents from countries where the disease is highly endemic and who are returning temporarily to their country of origin are at risk of contracting, importing and spreading hepatitis A. Vaccination is recommended by the French High Council of Public Health in this population and in any person intending to travel to a country where hygiene is poor and where hepatitis A is endemic. However, vaccination of such persons travelling as private individuals is not covered by National Health Insurance.

4.4 Target population

The target population (children aged 1 to 15 years) of the vaccine AVAXIM 80 U PEDIATRIQUE includes patients with cystic fibrosis and/or active chronic liver disease (in particular due to hepatitis B or C).

It must take into account:
- the incident target population;
- the target population for catch-up vaccination.

4.4.1 Incident target population (new subjects to be vaccinated)

Patients with cystic fibrosis and patients with active chronic liver disease (in particular due to hepatitis B or C)

- Cystic fibrosis
  The prevalence of cystic fibrosis is in the order of one in every 4000 births, i.e. about 200 new cases per year.

- Active chronic liver disease
  In 2008, according to general health insurance scheme data, 193 children aged 0 to 14 years were treated for the first time under ALD 6 (Affections de Longue Durée : Long Term Affections) “active chronic liver disease and cirrhosis”. Since the general health insurance scheme accounts for close to 80% of individuals covered by National Health Insurance, the number of children aged 0 to 14 years treated for the first time each year under ALD 6 is estimated at about 240.

10 HAS. Guide to long-term conditions (ALD). Cystic fibrosis: National diagnosis and treatment plan for a rare disease, 2006
4.4.2 Target population for catch-up vaccination

Patients with cystic fibrosis and patients with active chronic liver disease (in particular due to hepatitis B or C)

- Cystic fibrosis
  The number of cystic fibrosis patients in France is estimated at 6000\textsuperscript{12}. According to data from the French cystic fibrosis register, in 2006 one in every two patients was under 15 years of age, which corresponds to about 3000 patients\textsuperscript{13}.

- Active chronic liver disease
  In 2008, according to general health insurance scheme data, 1184 children aged 0 to 14 years were being treated under ALD 6 “active chronic liver disease and cirrhosis”\textsuperscript{14}. Since the general health insurance scheme accounts for close to 80\% of individuals covered by National Health Insurance, around 1500 children aged 0 to 14 years were being treated under ALD 6 in France.

The number of children aged 1 to 15 years likely to take part in catch-up vaccination against hepatitis A is estimated at about 4500.

4.5 Transparency Committee recommendations

The Transparency Committee recommends inclusion of AVAXIM 80 U PEDIATRIQUE in the list of medicines reimbursed by National Health Insurance and in the list of medicines approved for use by hospitals and various public services with the indications and the dosage of the Marketing Authorisation in the following populations: patients with cystic fibrosis (the prevention of hepatitis is essential in these patients at risk of hepatic complications), patients with active chronic liver disease, in particular due to hepatitis B and C.

4.5.1 Packaging: The packaging is appropriate for the prescription conditions.

4.5.2 Reimbursement rate: 65\%