HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

19 May 2010

HAVRIX 1440 U/1 ml ADULTES, suspension for injection in prefilled syringe. Hepatitis A virus (inactivated, adsorbed)

Box of 1 (CIP: 337 751-5)

Applicant: GLAXOSMITHKLINE

Hepatitis A virus, strain HM 175 (inactivated)[1, 2]..... 1440 U*
[1]Cultured on human diploid cells (MRC-5)
[2] Adsorbed on aluminium hydroxide (0,50 mg Al^{3+})
*Units measured according to the manufacturer's in-house method.

ATC code: J07BC02

List 1
Date of first Marketing Authorisation: 18 August 1994 – revision 15 July 2009

Medicine approved for use by hospitals

Reason for request: Inclusion on the list of medicines reimbursed by National Health Insurance for the populations recommended by the *Haut Conseil de la Santé Publique*.

Additional document: 2010 immunisation schedule[1]

Medical, Economic and Public Health Assessment Division

1 2010 immunisation schedule and guidelines issued by the *Haut Conseil de la Santé Publique*, BEH [weekly epidemiological bulletin] 14/15, 22 April 2010.

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Inactivated, adsorbed hepatitis A virus

1.2. Indication

“This vaccine is indicated for active immunisation against infection caused by hepatitis A virus.

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

Vaccination against viral hepatitis A is recommended in subjects at risk of exposure to the hepatitis A virus.

The persons likely to benefit from vaccination are determined in accordance with official guidelines.”

1.3. Dosage (see SPC)

“Adults over 15 years of age: the recommended dosage is 1 ml for each injection.

The standard immunisation schedule is one dose followed by a booster dose to be given preferably 6 to 12 months after the first injection. This second dose may, however, be given later than this: up to 5 years after the first dose.

Available data suggest that HAV antibodies persist at protective levels up to ten years after two doses of HAVRIX.”

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

AVAXIM 160 U, suspension for injection in prefilled syringe. Hepatitis A virus (inactivated, adsorbed): approved for hospital use, not reimbursed by National Insurance.

2.3. Medicines with a similar therapeutic aim (bivalent vaccines)

TWINRIX ADULTE, suspension for injection in prefilled syringe. Vaccine against hepatitis A (inactivated) and hepatitis B (ADNr) (HAB) (adsorbed): approved for hospital use, not reimbursed by National Insurance.

TYAVAX, suspension and solution for injection in a two-compartment prefilled syringe. Hepatitis A (inactivated, adsorbed) and typhoid (polysaccharide) vaccine: approved for hospital use, not reimbursed by National Health Insurance.

3. UPDATE OF AVAILABLE DATA

The applicant has submitted the results of three studies that evaluated the immunogenicity and tolerance of HAVRIX 1440 U/1 ml in:
- patients living in an institution for the disabled (Broggini *et al.*, 2002)
- patients with chronic liver disease (Keeffe *et al.*, 1998)
- patients who have received a liver transplant (Stark *et al.*, 1999).

and the results of a study that evaluated the clinical efficacy of the HAVRIX vaccine in preventing secondary infections in families with a reported case of hepatitis A (Sagliocca *et al.*, 1999).

GSK's application for inclusion on the list of medicines reimbursed by National Health Insurance pertains to the following populations, as defined in the current immunisation schedule guidelines:

- Specific recommendations:
  - Patients with cystic fibrosis and/or hepatobiliary pathologies likely to develop chronic liver disease (in particular due to hepatitis B or C or excessive alcohol consumption)
  - Male homosexuals
  - In the event of one or more cases of hepatitis A, hepatitis A vaccination is recommended in family members of the ill individual and in communities, whose members live in conditions of poor hygiene.
- Occupational risks:
  - Persons working with children who are not yet toilet-trained (e.g., persons working in day care centres, childminders)
  - Persons working in institutions for the disabled
  - Sewage-treatment workers
  - Workers involved in food preparation in the catering industry.

3.1. Summary: Data on the immunogenicity and protective efficacy in healthy adults in the general population (excerpt from the SPC)

"In clinical studies where the kinetics of the immune response have been studied, early and rapid seroconversion (antibody titre > 20 mIU/ml) was demonstrated in immunocompetent subjects after administration of a single dose of HAVRIX:

- in 79% of subjects from the 13th day
- in 86.3% of subjects from the 15th day
- in 95.2% of subjects from the 17th day
- in 100% of subjects from the 19th day.

It should be noted that this period of time is shorter than the average incubation period of the hepatitis A virus, which is about 4 weeks.
One month after the booster dose, all subjects were seropositive.

The efficacy of HAVRIX was evaluated during various community epidemics (Slovakia, United States, the United Kingdom, Israel and Italy) and it was demonstrated that vaccination with HAVRIX could help stop these epidemics.

The booster dose can be given up to 5 years later if it was not given 6 to 12 months after the first injection. Indeed, a study that compared antibody titres following administration of the booster dose 6 to 12 months and up to 5 years after the first injection demonstrated similar antibody titres.

The persistence of hepatitis A virus (HAV) antibodies 10 years after vaccination is not known. The available data suggest that antibody titres are stable at a protective level (> 20 mIU/ml) after 10 years.
Based on current data, there are no grounds for administering further booster doses in subjects who have already received two doses of the vaccine."

3.2. Immunogenicity in the following special populations: patients living in an institution for the disabled, patients with chronic liver disease, liver transplant patients

The applicant has submitted the results of three studies in adults that evaluated the immunogenicity and tolerance of HAVRIX 1440 U/1 ml in:
- patients living in an institution for the disabled (Broggini *et al.*, 2002)[2];
- patients with chronic liver disease (Keeffe *et al.*, 1998)[3];
- patients who have received a liver transplant (Stark *et al.*, 1999)[4].

Study by Broggini *et al*., 2002[2]

Main objective: to evaluate the immunogenicity and tolerance of HAVRIX 1440 U/1 ml in patients living in an institution for the disabled.

Methodology: open-label study carried out on 18 patients aged 23 to 49 years vaccinated with HAVRIX 1440 U/1 ml according to a 0-6 month schedule. The HAV antibody titre was measured one month after initial vaccination and one month after the booster dose six months later.

Results: 7 of the 18 patients developed antibodies one month after the first dose and all patients developed antibodies after administration of the second dose six months later.

Study by Keeffe *et al*., 1998[3]

Main objective: to evaluate the immunogenicity and tolerance of HAVRIX 1440 U/1 ml in adults with chronic liver disease.

Methodology: open-label, controlled study carried out on 475 patients divided into five groups:
- healthy subjects (group 1)
- patients with chronic hepatitis B (group 2)
- patients with chronic hepatitis B (groups 3 and 4)
- patients with other chronic liver disease not secondary to viral hepatitis (group 5).

Patients with clinical or laboratory signs of advanced liver disease were excluded.
The patients in groups 1, 2, 3 and 5 were vaccinated with HAVRIX 1440 U/1 ml according to a 0-6 month schedule and group 4 received a hepatitis B vaccine (Engerix B) according to a 0, 1, 6 month schedule.
The HAV antibody titre was measured 1, 2, 6 and 7 months after primary vaccination. The seroconversion threshold was set at 33 mIU/ml.

Results: The seroconversion rate (percentage of patients with an antibody titre greater than 33 mIU/ml) one month after primary vaccination was higher in the group of healthy subjects (group 1) than among patients with chronic hepatitis C (group 3) and patients with another

2 Broggini M, Speranza F, Agrifoglio L, et al., Hepatitis A vaccination in institutionalized mentally disabled patients. Riv It Biol Med 2002; 22: 1-3
3 Keeffe EB, Iwarson S, McMahon BJ, et al., Safety and immunogenicity of hepatitis A vaccine in patients with chronic liver disease. Hepatology 1998; 27: 881-6
4 Stark K, Günther M, Neuhaus R, et al., Immunogenicity and safety of hepatitis A vaccine in liver and renal transplant recipients. J Infect Dis 1999; 180: 2014-7

chronic liver disease not secondary to viral hepatitis (group 5) (seroconversion rate in healthy subjects: 93%; patients with chronic hepatitis C: 74%; patients with chronic liver disease not secondary to viral hepatitis: 83%; $p < 0.01$).

One month after the booster dose, the seroconversion rate was greater than 94%, with no difference between healthy subjects and patients with chronic liver disease.

Study by Stark *et al*., 1999[4]

Main objective: to evaluate the immunogenicity of HAVRIX 1440 U/1 ml in liver and renal transplant patients.

Methodology: open-label, controlled study carried out on 107 patients (39 liver transplant patients, 39 kidney transplant patients and 29 control subjects) vaccinated with HAVRIX 1440 U/1 ml according to a 0-6 month schedule. The HAV antibody titre was measured after each dose of vaccine. The seroconversion threshold was established at 33 mIU/ml.

Results: only the results for liver transplant patients are described here. After the first dose, the seroconversion rate (percentage of patients with an HAV antibody titre ≥ 33 mIU/ml) was 41% in the liver transplant patients and 90% in the control group.
One month after the booster dose, the seroconversion rate was 97% in the liver transplant patients and 100% in the control group (the GMT was 1306 mIU/ml in the liver transplant patients and 1596 mIU/ml in the control group; $p = 0.35$).

3.3. Protective efficacy in families with a reported case of hepatitis A (in an adult or child)

The applicant has submitted the results of a study that evaluated the clinical efficacy of the HAVRIX vaccine in the prevention of secondary infections in families with a reported case of hepatitis A (Sagliocca *et al*., 1999)[5].

Study by Sagliocca *et al*., 1999[5]

Objective: to evaluate the protective efficacy of the vaccine HAVRIX in families with a reported case of hepatitis A.

Methodology: randomised comparative study carried out in Italy between May and October 1997 in families (contact subjects) with a member, who had been hospitalised for hepatitis A (index cases).

Index cases were defined as patients with primary hepatitis A virus infection (positive IgM HAV antibody test, serum alanine aminotransferase at least twice the normal value, hospitalisation in the week following the appearance of symptoms of the disease) and were randomised into two groups:

- a group in which vaccination against HAV was suggested to contact subjects (family members aged 1 to 40 years)
- a group in which contact subjects were not vaccinated against hepatitis A.

The contact subjects in the vaccinated group were given an injection of HAVRIX (HAVRIX 1440 U/1 ml for adults and HAVRIX 720 U/0.5 ml for children under 11 years) in the 8 days after the onset of symptoms in the index case.

Among the contact subjects, HAV seronegative subjects were monitored for the 45-day follow-up period.
A diagnosis of secondary infection in contact subjects was based on the presence of IgM HAV antibodies at least two weeks after the onset of symptoms in the index case.

5 Sagliocca L. Efficacy of hepatitis A vaccine in prevention of secondary hepatitis A infection: a randomised trial. Lancet 1999; 353: 1136-39

Results:
A total of 146 eligible index cases were recruited and accepted for participation in the study: 71 patients associated with 197 contact subjects (of whom 173 had given their consent) in the vaccination group and 75 patients associated with 207 contact subjects (of whom 178 had given their consent) in the comparator group.
Among the contact subjects, 110 out of the 173 in the vaccination group and 102 out of the 178 in the comparator group were seronegative for HAV on inclusion in the study and had been monitored for the follow-up period of 45 days.

The number of secondary infections (IgM HA seroconversion) was 2/197 (1.0%) in the vaccinated group and 12/207 (5.8%) in the unvaccinated group.
The protective efficacy* of the vaccine was 82% (95% confidence interval (CI): 20-96).

(* incidence in the unvaccinated group – incidence in the vaccinated group / incidence in the unvaccinated group $\times$ 100)

3.4. **Adverse effects** (excerpt from SPC)

The tolerance profile presented below is based on data obtained from more than 5300 subjects included in clinical studies with HAVRIX.

The adverse effects reported most frequently were as follows:

Very common (frequency $\geq$ 1/10):
- irritability
- headache
- pain and redness at the injection site
- asthenia

Common (frequency ≥ 1/100 and < 1/10):
- loss of appetite
- drowsiness
- gastrointestinal symptoms (such as diarrhoea, nausea, vomiting)
- swelling at the injection site, malaise, fever (≥ 37.5°C), reaction at the injection site (e.g., induration).

3.5. Conclusion

HAVRIX 1440 U/1 ml induces the production of HAV antibodies at a protective level (HAV antibody titre > 20 mIU/ml) in 100% of immunocompetent subjects from the 19th day after the administration of a single dose of the vaccine.
The standard immunisation schedule is one dose followed by a booster dose to be given preferably 6 to 12 months after the first injection. This second dose may be given up to 5 years after the first dose.
The available data suggest that antibody titres are stable at a protective level after 10 years.
In persons with chronic liver disease and in liver transplant patients, despite a weaker vaccine response than in healthy subjects, the two-dose immunisation schedule (0-6 months) induces the production of a protective level of antibodies in more than 94% of vaccinated subjects.
In family members (contact subjects) of patients hospitalised due to hepatitis A (index cases), the protective efficacy* of the vaccine was 82% (95% confidence interval (CI): 20-96). This result was obtained from a study carried out in Italy in 1997 with a small number of participants.
(* incidence in the unvaccinated group – incidence in the vaccinated group / incidence in the unvaccinated group $\times$ 100)
A study was carried out on a very small number of patients living in an institution for the disabled (18 patients).

No data has been supplied by the applicant for the following populations: male homosexuals, persons working with children who are not yet toilet-trained, in institutions for the disabled, in sewage-treatment plants and persons involved in food preparation in the catering industry.

The protective efficacy of HAVRIX was evaluated during various community epidemics (Slovakia, the United States, the United Kingdom, Israel and Italy), in which it was demonstrated that vaccination with HAVRIX could help stop these epidemics. This vaccine is well tolerated.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Hepatitis A is usually a mild disease, although it can give rise to serious forms (sometimes fatal in patients with chronic liver disease), particularly in adults[6].
Vaccination aside, the basis for prevention is improving personal and collective hygiene.

The vaccine is a preventive therapy.

The efficacy (immunogenicity and protective efficacy)/adverse effects ratio of this product is high in patients with cystic fibrosis and active chronic liver disease, in particular due to hepatitis B and C.
The benefit of vaccination has not been demonstrated in clinical studies carried out in other populations.

There is no vaccine alternative reimbursed by National Insurance.

Public health benefit

Although normally a mild condition, particularly in children, hepatitis A can, in rare cases, develop into severe forms (fulminant hepatitis), particularly in patients with chronic underlying liver disease. In France 1204 cases were reported in 2008 through mandatory reporting, and 45% of these cases required hospitalisation[7]. 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[8]. The public health burden of hepatitis A is therefore low.

Given the steady increase in the susceptibility of the French population to the hepatitis A virus and the potential for hepatitis A-related decompensation in patients with chronic liver disease, preventing hepatitis A meets an identified public health need (Guidelines of the *Haut Conseil de la Santé Publique*, Public Health Law 2004).

The data on the efficacy of HAVRIX in populations at risk for complications (patients with active chronic liver disease) and targeted by the guidelines are essentially based on immunogenicity data or are descriptive in nature.

6 Reiss G, Keeffe EB. Review article: Hepatitis vaccination in patients with chronic liver disease. Aliment Pharmacol Ther 2004; 19: 715-27
7 InVS [French Health Monitoring Institute] data available at: http://www.invs.sante.fr/surveillance/hepatite_a/donnees_2008.htm retrieved 4 March 2010
8 Statistics on the medical causes of deaths, CépiDc at INSERM [National Institute of Health and Medical Research]. CépiDc: http://www.cepidc.vesinet.inserm.fr/

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

According to mandatory reporting[1], the principal risk factors are living outside metropolitan France (reported in 40% of cases) and the presence of hepatitis A-infected persons in the patient's family (reported in 50% of cases). The indirect impact of the vaccine on the spread of an epidemic can be only be considered low given the number of clusters observed in France (about 400 cases in 2008). The positive effect of vaccination on reducing the incidence of infections with hepatitis A has been established only in situations where the disease is highly endemic (Thailand) and in massive outbreaks (Alaska) and not in situations of limited outbreaks, such as those that occur in France. Moreover, there are no available comparative studies *versus* the implementation of preventive hygiene and dietary measures.

It is therefore uncertain whether the results of these studies can be applied to clinical practice, and doing so depends on whether adequate vaccination coverage is achieved in the populations targeted by the guidelines.

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

HAVRIX should help meet an identified public health need.

However, based on the current level of knowledge, the expected benefit public health benefit of HAVRIX in the populations recommended by the *Haut Conseil de Santé Publique* is hard to quantify.

The actual benefit of HAVRIX is substantial in patients with cystic fibrosis and 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 on an adequately large population and data from comparative studies *versus* the implementation of preventive hygiene measures.

HAVRIX 1440 U/1 ml ADULTES offers a moderate improvement in actual benefit (IAB level III) in terms of immunogenicity and tolerance 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 reiterates that the *Haut Conseil de la Santé Publique* considers generalised vaccination against hepatitis A in France to be disproportionate given the low incidence of the disease.

4.3.1. Guidelines listed in the 2010 immunisation schedule (adults)

According to the 2010 immunisation schedule[9], preventive vaccination against hepatitis A is recommended in the following populations:

9 2010 Immunisation schedule

Specific risks (other than occupational risks):

- Patients with cystic fibrosis and/or chronic hepatobiliary pathologies likely to develop into chronic liver disease (in particular due to hepatitis B or C or excessive alcohol consumption)
- Recommendations on vaccination regarding a case of hepatitis A:
  . in the immediate family
  . in communities living in conditions of poor hygiene
- Male homosexuals

Occupational risks:

- working with children who are not yet toilet-trained (e.g., people working day care centres and childminders)
- working in institutions for the disabled
- working in sewage-treatment
- working in food preparation in the catering industry.

4.3.2. Therapeutic use of the HAVRIX vaccine in preventing hepatitis A in adults in the context of reimbursement by National Health Insurance

The Transparency Committee considers that reimbursement by National Insurance of the HAVRIX adult vaccine 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:

- Persons working with children who are not yet toilet-trained, in institutions for the disabled, in sewage-treatment plants and in food preparation for the catering industry may be treated under their employer's responsibility in accordance with article R4426-6 of the French Labour Code: "If suggested by the occupational physician, the employer should advise workers who are not vaccinated against biological pathogens to which they are or might be exposed to receive the appropriate vaccinations at the employer's expense."

- Resorting to vaccination in the event of an epidemic in schools or in institutions for mentally or physically disable people is a decision that must be made by the regional or national authorities following a survey identifying conditions of poor hygiene for which lasting improvement is difficult to achieve.

4.4. Target population

The adult target population (over 15 years of age) for the HAVRIX 1440 U/1 ml vaccine comprises 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 (new subjects to be vaccinated);
- the target population for "catch-up" vaccination.

4.4.1. Incident target population (new subjects to be vaccinated)

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

In 2008, 20,326 beneficiaries of the general health insurance scheme were treated under ALD 6 "active chronic liver disease and cirrhosis"[10]. Since the general health insurance scheme accounts for close to 80% of individuals covered for chronic conditions (ALD stands for *Affection de Longue Durée*, or long-term illnesses) by National Insurance, the number of persons treated for the first time each year under ALD 6 is estimated at about 25,000.

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

In France there are some 6000 cystic fibrosis patients[11]. According to data from the French cystic fibrosis register, in 2006 one in every two patients was over 15 years of age, which corresponds to about 3000 patients[12].

- Active chronic liver disease

In 2008, 156,484 persons registered with the general health insurance scheme were treated under ALD 6 "active chronic liver disease and cirrhosis"[13]. Since the general health insurance scheme accounts for close to 80% of individuals covered against chronic conditions (ALD) by National Insurance, some 182,000 persons were being treated under ALD 6 in France.

The adult population (aged over 15 years) likely to take part in catch-up vaccination against hepatitis A is estimated at about 185,000 persons.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance in the indications and at 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%

10 French national health insurance (CNAMTS). http://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/donnees-statistiques/affection-de-longue-duree-ald/incidence/ald-30-en-2008.php (table IV)

11 French Cystic Fibrosis Association. http://vaincrelamuco.org/ewb_pages/e/etre-muco.php.

12 Fighting cystic fibrosis, National Institute of Demographic Studies. French cystic fibrosis register. Summary of 2006 data, INED 2009.

13 Païta M et al., Les bénéficiaires d'affection de longue durée au 31 décembre 2008 [Persons with long-term illness benefitting from 100% reimbursement for care as of 31 December 2008]. Points de repère No. 27, CNAMTS, December 2009.