HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

19 May 2010

HAVRIX NOURRISSONS ET ENFANTS 720 U/0.5 ml, suspension for injection in prefilled syringe. Inactivated, adsorbed hepatitis A vaccine

Box of 1 (CIP: 347 604-5)

Applicant: GLAXOSMITHKLINE

Hepatitis A virus, strain HM 175 (inactivated)[1, 2] ..... 720 U*
[1]Cultured on human diploid cells (MRC-5)
[2] Adsorbed on aluminium hydroxide (0.25 mg Al^{3+})
*Units measured according to the manufacturer's in-house method.

ATC code: J07BC02

List 1
Date of first Marketing Authorisation: 6 August 1998 – 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)

"Children aged 1 to 15 years: the recommended dosage is 0.5 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

VAQTA 25 U/0.5 ml: approved for hospital use, not reimbursed by National Health Insurance.

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

TWINRIX ENFANT, 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 Health Insurance.

3. UPDATE OF AVAILABLE DATA

The applicant has submitted the results of one study that evaluated the immunogenicity and safety of HAVRIX 720 U/0.5 ml in children with chronic liver disease (Feirreira *et al.*, 2003) and the results of two studies that evaluated the protective efficacy of vaccination with HAVRIX 720 U /0.5 ml:
- in children born to parents originally from countries where the disease is highly endemic (Sonder *et al.*, 2006)
- 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:
- Children living in homes and institutions for disabled children
- Patients with cystic fibrosis and/or hepatobiliary pathologies likely to develop chronic liver disease (in particular due to hepatitis B or C),
- Children at least one year of age with family members from a country where the disease is highly endemic when these children are likely to visit that country,
- 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.

3.1. Summary: Data on the immunogenicity and protective efficacy in healthy children 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 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.

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 a special population, in children with chronic liver disease

The applicant has submitted the results of a study that evaluated the immunogenicity and safety of HAVRIX 720 U/0.5 ml in children with chronic liver disease (Feirreira *et al.*, 2003)[2].

Main objective: to evaluate the immunogenicity and safety of HAVRIX 720 U/0.5 ml in children and adolescents aged 1 to 16 years with chronic liver disease.

Methodology: open-label comparative study on 34 children with chronic liver disease (mean age 7 ± 4.86 years) and in 55 healthy subjects in the comparator group (mean age 4.8 ± 2.7 years) who had received two doses of HAVRIX 720 U/0.5 ml at 0 and 6 months.

Results: seroconversion rates (HAV antibody titre ≥ 33 mIU/ml) were significantly lower in the children with chronic liver disease: the seroconversion rate 1 month after the first dose was 76% (geometric mean titre/GMT: 107.7 mIU/ml) in the group with chronic liver disease and 94% (GMT: 160.77 mIU/ml) in the comparator group ($p < 0.05$).

One month after the second dose, the seroconversion rate was 97% in the group with chronic liver disease and 100% in the comparator group (NS).

The geometric mean titre was lower in the group with chronic liver disease than in the comparator group (GMT: 812.40 versus 2344.90 mIU/ml, $p = 0.001$).

3.3. Protective efficacy in children born to parents originally from countries where the disease is highly endemic and in families where there has been a reported case of hepatitis A

The applicant has submitted the results of two studies in children that evaluated the protective efficacy of vaccination with HAVRIX 720 U/0.5 ml:
- in children born to parents originally from countries where the disease is highly endemic (Sonder *et al.*, 2006)[3]
- in families where there has been a reported case of hepatitis (Sagliocca *et al.*, 1999)[4]

Study by Sonder *et al.*, 2006[3]

Starting in 1998, the Netherlands launched a vaccination campaign targeting children under the age of 16 years born to parents originally from countries where the disease is highly endemic (in particular Turkey and Morocco) when these children are likely to visit these countries.

Objective: to retrospectively evaluate the impact of the annual vaccination campaign introduced in 1998 targeting children under the age of 16 years born to parents originally from countries where the disease is highly endemic when these parents are planning a summer visit with their children to their country of origin.

2 Ferreira CT. *et al.,* Immunogenicity and Safety of Hepatitis A Vaccine in Children With Chronic Liver Disease. J Ped Gastoenterol Nutrition 2003; 37: 258-61).
3 Sonder JGB, Bovée LPMG, Baayen TD, Coutinho RA, Van Den Hoek JAR. Effectiveness of a hepatitis A vaccination program for migrant children in Amsterdam; The Netherlands. 1992-2004. Vaccine 2006; 24: 4962-8.
4 Sagliocca L. Efficacy of hepatitis A vaccine in prevention of secondary hepatitis A infection: a randomised trial. Lancet 1999; 353: 1136-39

Methodology: the study was carried out in Amsterdam. A retrospective analysis was carried out of the number of vaccinations between 1992 and 2004, the number of cases of hepatitis A reported during this period, and the most probable source of infection.

Results: of the total number of cases reported in Amsterdam between 1992 and 2004, 28% were associated with a visit to a region where the disease is endemic. Of the cases of hepatitis A following a visit to a region where the disease is endemic, 66% were observed in children under the age of 16 years of Moroccan or Turkish origin.

After the 1998 introduction of the vaccination campaign, the following was observed:

- a reduction in cases of hepatitis A in subjects travelling to countries where the disease is highly endemic: the incidence ratio was 1.00 (0.94-1.05) before 1998 versus 0.87 (CI 0.81-0.93) after 1998 ($p < 0.014$).
- a reduction in cases of hepatitis A in the families of infected individuals and in schools:
    . the incidence ratio in the families of infected individuals was 0.96 (0.88-1.03) before 1998 versus 0.61 (CI 0.51-0.72) after 1998 ($p < 0.001$).
    . the incidence ratio in schools was 0.92 (0.86-0.99) before 1998 versus 0.67 (CI 0.58-0.77) after 1998 ($p = 0.001$).

Levels of immunisation coverage were 25 to 40% (depending on age and on the origin of the community) from 2001 to 2004.

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

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.

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.

Of 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 × 100)

3.4. Adverse effects (see SPC)

The safety 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 ≥ 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

Nearly 100% of vaccinated healthy children (aged 1 to 15 years) develop a protective antibody titre within one month following administration of the first dose of the vaccine HAVRIX. 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.

In children with chronic liver disease, despite a weaker vaccine response than in healthy subjects after administration of the first dose of vaccine, it was shown that the two-dose immunisation schedule (0-6 months) induces the production of a protective level of antibodies in more than 97% of vaccinated children.
A retrospective analysis has demonstrated the impact of a vaccination programme on children under the age of 16 born to parents originally from a country where the disease is highly endemic when these children are likely to return there.
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 × 100)

The applicant has not supplied any data for children living in homes and institutions for disabled children.

The 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 that in exceptional cases can be fatal.
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 children living in homes and institutions for disabled children.

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[5]. 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[6]. 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).

5 InVS [French Health Monitoring Institute] data available at: http://www.invs.sante.fr/surveillance/hepatite_a/donnees_2008.htm, retrieved 4 March 2010
6 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 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.
In the absence of data on the proportion of decompensation cases 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 NOURRISSONS ET ENFANTS 720 U/0.5 ml 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 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 (children))

According to the 2010 immunisation schedule[7], preventive vaccination against hepatitis A is recommended in the following populations:
- Children living in homes and institutions for disabled children
- Patients with cystic fibrosis and/or hepatobiliary pathologies likely to develop chronic liver disease (in particular due to hepatitis B or C),
- Children at least one year of age with family members from a country where the disease is highly endemic when these children are likely to visit that country,
- 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.

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

The Transparency Committee considers that reimbursement by National Insurance of the HAVRIX NOURRISSONS ET ENFANTS 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 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.

- Unvaccinated children born in France to immigrant parents from countries where the disease is highly endemic who are returning temporarily to their country of origin are at risk of contracting, importing and spreading hepatitis A. Vaccination is recommended by the HCSP in this population and for any person intending to travel to a country where hygiene is poor and where hepatitis A is endemic[8]. However, National Health Insurance does not reimburse vaccinations for people in the latter group.

4.4. Target population

- The target population (children aged 1 to 15 years) for the HAVRIX 720 U/0.5 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;
- the target population for catch-up vaccination.

7 2010 immunisation schedule and guidelines issued by the *Haut Conseil de la Santé Publique*, BEH [weekly epidemiological bulletin] 14/15, 22 April 2010.
8 Health recommendations for travellers: http://www.invs.sante.fr/beh/2009/23_24/index.htm

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 of the order of one in every 4000 births[9], 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* no. 6 "active chronic liver disease and cirrhosis"[10] (ALD stands for *Affection de Longue Durée*, or long-term illnesses). 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* no. 6 is estimated to be approximately 240.

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 to be 6000[11]. According to data from the French cystic fibrosis registry, in 2006 one in every two patients was under 15 years of age, which corresponds to about 3000 patients[12].

- 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"[13]. Since the general health insurance scheme accounts for close to 80% of individuals covered by National Health Insurance, some 1500 children aged 0 to 14 years were being treated under ALD 6 in France.

4.5. Transparency Committee recommendations

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

9 HAS. Guide to long-term conditions (ALD). Cystic fibrosis: National diagnosis and treatment plan for a rare disease, 2006

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, French Institute of Demographic Studies. French Cystic Fibrosis registry. Summary of 2006 data, INED 2009.

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