SUMMARY FOR BASIS OF APPROVAL

REFERENCE NUMBER: 92-0465

DRUG LICENSED NAME: HEPATITIS A VACCINE (INACTIVATED)

MANUFACTURER SMITHKLINE BEECHAM BIOLOGICALS

DRUG TRADE NAME: HAVRIX™

Havrix™ (Hepatitis A Vaccine, Inactivated) is a whole-virion formaldehyde inactivated alum-adsorbed vaccine indicated for active immunization against hepatitis A virus (HAV).

I. Indications For Use

Havrix™ is indicated for active immunization of adults and children two years of age and older against infection caused by hepatitis A virus (HAV).

Havrix™ will not prevent infection caused by other agents such as hepatitis B virus, hepatitis C virus, hepatitis E virus or other pathogens known to infect the liver.

Immunization with Havrix™ is indicated for those people desiring protection against hepatitis A. **Primary immunization should occur** at least two weeks prior to expected exposure to HAV. Individuals who are, or will be, at increased risk of infection by HAV include:

Travelers.
Persons traveling to areas of higher endemicity for hepatitis A. These areas include, but are not limited to, Africa, Asia (except Japan), the Mediterranean basin, Eastern Europe, the Middle East, Central and South America, Mexico, and parts of the Caribbean.

Military personnel.

People living in, or relocating to, areas of high endemicity.

Certain ethnic and geographic populations that experience cyclic

hepatitis A epidemics such as:
Native peoples of Alaska and the Americas.

Others.
Persons engaging in high risk sexual activities, such as male homosexuals.
Users of illicit injectable drugs.
Residents of communities experiencing an outbreak of hepatitis A.

Although the epidemiology of hepatitis A does not permit the identification of other specific populations at high risk of disease, outbreaks of hepatitis A or exposure to hepatitis A virus have been described in a variety of populations in which Havrix™ may be useful:

- Certain institutional workers (e.g., caretakers for the developmentally challenged)
- Employees of child day-care centers
- Laboratory workers who handle live hepatitis A virus
- Handlers of primate animals that may harbor hepatitis A virus

People exposed to hepatitis A.
For those requiring both immediate and long-term protection, Havrix™ may be administered concomitantly with IG. When this is done, an average two-fold reduction in the peak titer of hepatitis A-specific antibodies arising from active immunization may be expected. This effect of IG on the immunogenicity of Havrix™ may be alleviated by the administration of a booster dose of Havrix™.

II. Dosage Forms, Route of Administration and Recommended Dosage

Havrix™ is supplied as a sterile suspension of inactivated hepatitis A virus for intramuscular injection; viral antigen content is referenced to a standard using an enzyme linked immunosorbent assay (ELISA), and is therefore expressed in terms of ELISA Units (EL.U.).

Each 1 mL adult dose of vaccine consists of not less than 1440 EL.U. of viral antigen, adsorbed on 0.5 mg of aluminum as aluminum hydroxide.

Each 0.5 mL pediatric dose of vaccine consists of not less than 360 EL.U. of viral antigen, adsorbed onto 0.25 mg of aluminum as aluminum hydroxide.

The vaccine preparations contain 0.5% (w/v) of 2-phenoxyethanol as a preservative. **Other excipients are: amino acid supplement (0.3% w/v)** in a phosphate-buffered saline solution and polysorbate 20 (0.05 mg/mL). The vaccine also contains MRC-5 cellular proteins [redacted] hepatitis A viral antigens; each 720 EL. U. contains not more than [redacted]

The doses and vaccination schedules for Havrix™ administration are as follows:

Adults >18 years:	A single primary dose of 1440 ELISA Units (EL.U.) with a booster at 6-12 months
Children 2-18 years:	A two dose primary course of 360 EL.U. at 0 and 1 month with a booster at 6-12 months

III. Manufacturing and Controls

A. The virus (strain HM-175) is propagated in MRC5 human diploid cells, the manufacturing process being based on the seed lot principle. The virus strain, which was isolated from [redacted] was adapted to replicate in [redacted] cells at the National Institutes of Health in Bethesda. Thereafter it was adapted to grow in MRC-5 cells to generate master seed stock, working seed batch, and inoculum. The virus is purified and inactivated by treatment with formalin before it is adsorbed onto aluminum during the formulation process. The antigen (HAV) content is referenced to a standard using an ELISA. The dose is therefore expressed in terms of activity in ELISA Units (EL.U.).

The manufacturer provided adequate information to explain each of the steps in the manufacturing process. The controls for manufacturing procedures, which include specifications and test methods in process and on final product give sufficient assurance of identity, quality, purity and potency.

The manufacturer submitted samples and protocols for [redacted] lots; all lots met the release specifications established by the manufacturer.

B. Stability Studies

Anti-HAV antibody titers were determined by [redacted] and potency (ED_{50}) was determined by [redacted] of the HAV-specific antibody content of sera from [redacted] mice immunized with successive [redacted] dilutions of vaccine. Subsequently, an in vitro potency assay was developed to replace the mouse potency assay. In the in vitro assay, [redacted] and measured by ELISA. Stability of lots could also be shown using this method. Data were presented on the following production lots: [redacted] lots of 720 EL.U./mL monodose vial [redacted], [redacted] lots of 720 EL.U./mL pre-filled syringe [redacted], [redacted] lots of 1440 EL.U./mL monodose vial [redacted] lots of 1440 EL.U./mL pre-filled syringe [redacted] and [redacted] lots of 360 EL.U./0.5mL monodose vial [redacted]

These data support the recommended expiration date of 24 months from the filling date with storage at 2-8°C.

C. Validation

All major equipment, analytical methodology and critical manufacturing conditions and processes have been appropriately validated by SmithKline Beecham Biologicals at the Rixensart, Belgium facilities and found to be adequate for regulatory purposes.

D. Labeling

The label states the non-proprietary name ("Hepatitis A vaccine, inactivated") and the proprietary name ("Havrix™") of the product. The proprietary name is not in conflict with the tradename of any other drug.

Labels and labeling have been reviewed for compliance with 21 CFR 610.60, 610.61, 610.62, 201.56 and 201.57 and have been

found satisfactory.

Container labels contain a warning which indicates the following, "Shake well. For intramuscular use only. Store at 2° to 8° C (36° to 47 F. Do not freeze"

Carton labels also state that the product should not be frozen and should be discarded if frozen. A cautionary statement notes "Federal law prohibits dispensing without prescription". For the dosage, a statement referring to the accompanying prescribing information is included.

The package insert (attached) contains appropriate statements regarding product description, clinical pharmacology, indications and usage, contraindications, warnings, adverse reactions, dosage and administration, storage and handling conditions, and how supplied.

E. Establishment inspection

A pre-license inspection of the SmithKline Beecham Biologicals production facilities in Belgium was conducted August 30th to September 2nd 1993. The facility is considered to be in compliance with current GMP regulations.

F. Environmental Impact Analysis Report

In accordance with 21 CFR 25.31a, an environmental assessment was prepared. No potential adverse environmental impact is expected from the manufacture and use of Havrix™. The information supports a finding of no significant impact on the environment.

IV Pharmacology

The Clinical Pharmacology section of the package insert adequately describes the pertinent information contained herein under part IV.

A. Pharmacological Profile

The hepatitis A virus (HAV) belongs to the picornavirus family.

Only one serotype has been described. Havrix™ (Hepatitis A Vaccine, Inactivated) is a whole virion formaldehyde inactivated alum-adsorbed vaccine indicated for immunization against hepatitis A virus.

Administration of two doses of Havrix™ 720 EL.U. (in adults at month 0 and 1), 2 doses of Havrix™ 360 EL.U. (in children at months 0 and 1) or one dose of Havrix™ 1440 EL.U. (in adults at month 0) resulted in HAV specific seroconversion (anti-HAV titer >20 mIU/mL in a standardized ELISA) in over 95 % of vaccinees (Table 1). The GMTs induced by the vaccine using all three schedules were similar and were substantially in excess of those achieved using IG. Following the administration of the booster at month 6-12, there was an average ten-fold rise in titer of antibodies measured by ELISA (see also section V). Antibodies elicited by Havrix™ immunization had neutralizing activity in vitro, as measured by the [redacted] Test [redacted]) or a modified version of this assay using ELISA (SB HAV NT). For example, in one study an ELISA-Ig titer >500 mIU/mL was 85% correlated with a neutralizing antibody titer of >80 in the [redacted] Detectable neutralizing antibodies persisted through administration of the booster dose. For comparison, ELISA antibody titers as low as 20 mIU/mL, passively acquired by administration of IG, are associated with protection from HAV disease in vivo in both humans and chimpanzees.

[redacted] neutralizing monoclonal antibodies [redacted] were selected to demonstrate the HAV antigenic specificity of the immune response. These antibodies are directed against two distinct neutralizing epitopes on HAV. When combined, they inhibit binding to virus of HAV-specific antibodies in sera from patients convalescing from naturally acquired HAV infection, in a [redacted] ELISA. Sera from vaccinated volunteers was similarly shown to contain antibodies to epitopes recognized by these two monoclonal antibodies. Thus the quality of the immune response to Havrix™ appears to parallel that resulting from natural infection. Furthermore, rough correlation of results of the [redacted] with those of the ELISA-Ig suggest that virus neutralizing antibodies are a major fraction of the virus-binding antibodies measured in ELISA.

B. Summary of Preclinical Studies

Preclinical studies were focused on demonstrating the absence of toxicity, immunogenicity, and protective efficacy (see Table 2 for a summary of the studies performed).

To demonstrate the protective efficacy of hepatitis A vaccine, studies in two susceptible non-human primate species, chimpanzees and marmosets were conducted. **All primates which** responded to the vaccine, independent of vaccine dose, were protected against hepatitis A when challenged intravenously with wild type HM175 virus. **Chimpanzees which were actively** immunized were not only protected against disease but also failed to exhibit any evidence of infection, save for the delayed appearance of low titers of **IgM-class** HAV-specific antibodies, undetectable by the standard [redacted] test, in two of four animals tested.

In these models, an IgM response by [redacted] was invariably linked with disease.

Anti-HAV gamma globulin stimulated by vaccination of volunteers with inactivated HAV is capable of inducing passive immunoprophylaxis in chimpanzees against an intravenous challenge with HAV. **Unlike actively immunized chimpanzees,** passively immunized animals became infected after intravenous **challenge. This observation is comparable to the experience with** IG in man where it has been demonstrated that infection occurs in the absence of disease.

Vaccinated marmosets, in contrast with vaccinated chimpanzees, were protected against disease but not against initiation of infection as demonstrated by the presence of viral antigen in the liver, when wild type HAV was administered intravenously. However, viral replication was limited to the extent that virus was not excreted in the stools at detectable levels. When marmosets were challenged orally with HAV, all animals that responded to the vaccine were protected against both infection (by all criteria other than a weak anamnestic immune response) and disease.

The vaccinated non-human primates exposed to hepatitis A were protected against disease and did not excrete virus. **Therefore, it**

is likely that human vaccinees will not transmit the virus to susceptible contacts.

V. Medical

A. General Information

Hepatitis A (HA) is caused by a non-enveloped RNA virus that belongs to the picornavirus family. HAV is transmitted primarily by fecal-oral spread via person to person contact. Common source outbreaks have also been described. The incidence of disease is higher in developing countries and transmission is facilitated in areas of poor sanitation. An estimated 75,000 people each year present with clinical hepatitis A in the USA of whom 15% are hospitalized (1983-1987 figures). An annual loss of 300 million dollars has been attributed to this disease in the USA. The severity of disease is correlated with increasing age of the infected individual.

Pooled IG confers passive protection against hepatitis A. Protection is temporary and repeat administration is required at 3 to 5 month intervals to maintain protection.

Havrix™ induces specific humoral anti-HAV antibodies. Clinical pharmacological studies suggest that the immune response to Havrix™ is indistinguishable from that conferred by IG. In contrast to the temporary protection afforded by IG, the active immunity induced by Havrix™ is certain to be of far greater duration.

B. Overview of Clinical Studies

Forty-three studies were conducted worldwide as part of SmithKline Beecham Biologicals Havrix™ clinical development plan in support of licensure. A tabulation of all clinical studies conducted is provided in Table 3 (a-c).

The clinical program adequately described and demonstrated:

- the clinical tolerance to the vaccine and safety of the

vaccine

- the optimal dose level, the appropriate amount of adjuvant, and evaluation of suitable vaccination schedules
- the antibody response, in terms of quality of antibodies produced as well as seroconversion rates and antibody titers
- the reactogenicity in terms of the type, incidence and intensity of specified solicited local and general reactions
- the lot-to-lot consistency of commercial scale production lots in terms of reactogenicity and immunogenicity
- the protective efficacy of the vaccine in an extensive controlled field efficacy study
- ability to coadminister Havrix™ with IG or hepatitis B vaccine, Engerix®-B. Preliminary evidence also indicates that co-administration of a wide variety of other vaccines does not interfere with the immune response to Havrix™. Data are not yet available to indicate the converse, that Havrix™ immunization has no effect on the immune response to other vaccines, save for hepatitis B vaccine
- favorable comparison of anti-HAV titers with those conferred by IG
- immunogenicity in older subjects (>40 years)

The first clinical studies were initiated in December 1988 with pilot lots of the inactivated HM175 candidate vaccine. Four studies in adult subjects were undertaken to choose the dose of antigen to be used for vaccine development, determine an appropriate aluminum hydroxide content per dose and make a preliminary assessment of the clinical tolerance to the vaccine. The formulation of the vaccine at that time was set at 720 EL.U. of viral antigen in a dose volume of 1 mL.

The 720 EL.U./mL formulation was investigated in 21 non-US and 7 US trials in which Havrix™ was administered to adults in a 2- or 3-dose primary course followed by a booster. These data are considered as supportive.

Subsequently studies demonstrated that 1440 EL.U. (0, 6 months, i.e. single primary dose) administered to adults elicited an earlier response by day 15 and thereafter a similar antibody profile to that elicited by the 720 EL.U. dose/schedule (0,1 and 6 months).

A dose of 360 EL.U. was tested in children according to a primary vaccination schedule of 2 doses one month apart with a booster at month six. Seven studies were carried out to evaluate the vaccine in infants and children in order to make a critical evaluation of the safety and immunogenicity in that population and to establish the protective efficacy of Havrix™.

Table 4 summarizes the number of subjects who were enrolled and included in analyses of reactogenicity and immunogenicity.

C. Immunogenicity

The immunogenicity of the vaccine was routinely evaluated using an ELISA inhibition test developed by the sponsor. The quality of the antibodies developed (specific IgM, neutralizing antibodies) was evaluated in random samples of the populations enrolled in the studies for the 1440, 720 and 360 EL.U. dose levels (see also section IV). [redacted] of native MRC-5 cellular proteins using sera from Havrix™-immunized volunteers as probe failed to reveal evidence that the vaccine elicited a significant immune response to non-viral protein antigens contained in the formulation.

1440 EL.U. Dose: A total of 450 of the 494 volunteers enrolled in three pivotal studies of 1440 EL.U. were eligible for analysis of immunogenicity. Table 5a shows the overall analysis of immunogenicity following primary vaccination. The vaccine induced 88.1% seroconversion by day 15 and 98.9% of the originally seronegative subjects had seroconverted by one month after vaccination. At this point the GMT of anti-HAV antibodies was 466 mIU/mL (95% CI : 429-506 mIU/mL). This level of anti-HAV is similar to that obtained 1 month after a 2-dose primary vaccination (0 and 1 month schedule) with the 720 EL.U. dose of Havrix™: 517 mIU/mL (95% CI : 485-541 mIU/mL).

The GMTs obtained after the primary course of Havrix™ (1 dose of 1440 EL.U. or 2 doses of 720 EL.U.) are several times higher than those expected following receipt of IG, which is considered to be protective. For example, in one clinical study where 2.5 to 5 times the standard dose of IG was administered, the GMT five days after immunization was 146 mIU/mL, 77 mIU/mL at month 1 and 63 mIU/mL at month 2.

At month 6, just prior to the administration of the booster, seropositivity in the 261 subjects evaluated was 93.1% (Table 5b). The booster dose elicited a 23-fold increase in the GMT - from 189 mIU/mL to 4383 mIU/mL (range of individual titers: 3318 to 5925 mIU/mL) - and all vaccinees were seropositive at month 7.

720 EL.U. Dose: In the 2,125 subjects who received vaccine according to a 0, 1 month primary vaccination schedule in non-US trials, 95.7% of the initially seronegative vaccinees had seroconverted and the GMT was 304 mIU/mL. One month after the second dose, the seropositivity rate was 99.8%. The GMT was 517 mIU/mL. A booster dose administered at month 6 elicited a vigorous anamnestic response with GMTs rising approximately one order of magnitude. The effect of the booster was greater if the timing of the booster was delayed to 12 months. Similar results were found in the US trials.

Immune response in older adults:
Two studies were carried out to look at immune response in adults 40 years of age and older. Age was not found to be a confounding factor in terms of seroconversion but younger subjects responded with higher titers of anti-HAV. The difference in titers was not considered to be clinically relevant and thus the same dose and schedule is recommended for all adults > 18 years.

Simultaneous administration with IG or Engerix-B: Havrix™ may be administered concomitantly with IG, although studies indicate that the ultimate antibody titer obtained is likely to be lower than when the vaccine is given alone. Havrix™ has been administered simultaneously with Engerix-B (Hepatitis B Vaccine, recombinant) without interference with their respective

immune responses.

360 EL.U. Dose in Children: The clinical data in children were obtained from 7 studies in which all subjects were vaccinated according to a primary vaccination schedule of 0 and 1 month. The booster dose was administered at month 6 or 12. Analysis of immunogenicity was carried out in 763 children from five immunogenicity studies, and are shown in Table 6.

The vaccine induced seroconversion in 95.4% of subjects one month after the first dose and a GMT of 179 mIU/mL. The second dose one month later increased the proportion of seropositive subjects to 100% and the GMT to 483 mIU/mL (range: 197-660 mIU/mL). Just prior to the booster dose, all subjects tested were still seropositive, and the GMT was 308 mIU/mL.

The booster induced an increase in GMT to 3831 mIU/mL (95% CI: 3419 to 4293 mIU/mL). A blood sample taken at month 12 showed that all subjects tested were seropositive and had a GMT of 1069 mIU/mL (range: 3388 to 4643 mIU/mL).

Immunogenicity data obtained in the protective efficacy field trial are included below.

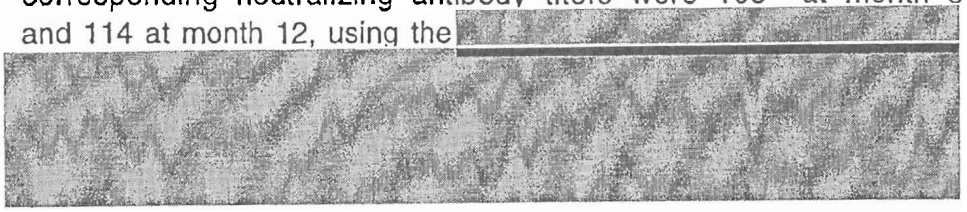
D. Protective Efficacy

The protective efficacy study was undertaken in 40,119 children who were allocated to receive either Havrix™ (360 EL.U. pediatric formulation) or a control vaccine (Engerix®-B, hepatitis B vaccine, recombinant; 10 µg/0.5 mL) at months 0, 1 and 12 in a random, double-blind study. The vaccinees were placed under clinical surveillance from month 4 to day 386. The protective efficacy against hepatitis A was determined by comparison of rates of HAV infections recorded during the surveillance of the vaccine group and the control group. Hepatitis A infections were defined as illness resulting in school absences of 2 or more days, serum alanine aminotransferase (ALT) of 45 U/L or greater, and a positive result for serum IgM to HAV in ill children with ALT elevations.

There were no serious adverse events reported which were attributable to the vaccine despite administration of more than

109,000 doses of Havrix™.

Among a subset of recipients of 2 doses of Havrix™ (0 and 1 month) who were initially seronegative (n= 239), 93.7% were seropositive by ELISA with a GMT of 200 mIU/mL. Immediately prior to booster at month 12, 93.3% were still seropositive with a GMT of 187 mIU/mL. This antibody response is consistent with those found in other pediatric and adult populations. The corresponding neutralizing antibody titers were 105 at month 8 and 114 at month 12, using the



Applying the criteria for hepatitis A infection as defined in the protocol, 34 cases of clinical hepatitis A were detected: 2 in the Havrix™ and 32 in the control vaccine groups, respectively. The two cases in the Havrix™ group were mild both in terms of biochemical and clinical indices of hepatitis A disease. Thus the calculated efficacy rate for prevention of clinical hepatitis A was 94% (95% confidence intervals 83% to 98%). In a post hoc analysis of the data from this trial, the use of the standard assay to confirm acute HAV infection in vaccinees was questioned. Since vaccinees might have had a modified or absent IgM response to subsequent natural infection as part of an anamnestic immune response to viral antigens, the possibility was raised that acute HA infections in vaccinees might have been missed. This would result in a falsely high estimate of the efficacy of the vaccine. (This consideration was made more significant, because the number of ill children with ALT elevations in the vaccinated group was not different from that in the control group.) Subsequently, additional data were presented which suggested that up to 3 ill vaccinees who were negative by the standard assay may have been acutely infected with HAV. The status of these latter children could not be determined with certainty. In this "worst case" analysis (5 total cases of acute HA in the vaccine group vs. 32 total in the control group), the efficacy of the vaccine was still calculated at 84%. These additional suspected (up to 3) acute HA infections in vaccinees were extremely mild compared to those in controls, when ALT levels and clinical history in the two groups were compared.

In school outbreak investigations performed as part of the trial, 26 clinical cases of hepatitis A were identified of a total of 34 occurring in the trial as a whole (using the standard case definition). No cases occurred in Havrix™ vaccinees.

E Safety

During clinical trials involving more than 26,000 individuals receiving doses ranging from 360 EL.U. to 1440 EL.U. and during extensive postmarketing experience, Havrix™ has been generally well tolerated. As with all pharmaceuticals, however, it is possible that expanded commercial use of the vaccine could reveal rare adverse events not observed in clinical studies.

The frequency of solicited adverse events tended to decrease with successive doses of Havrix™. Most events reported were considered by the subjects as mild and did not last for more than 24 hours.

Of solicited adverse events in clinical trials, the most frequently reported by volunteers was injection site soreness (56% of adults and 15% of children). However, less than 0.5% of soreness was reported as severe. Headache was reported by 14% of adults and less than 5% of children. Other solicited and unsolicited events occurring during clinical trials are as follows:

Incidence of 1% to 10% of Injections
Local reactions at injection site: induration, redness, swelling.
Body as a Whole: fatigue, fever (>37.5°C), malaise.
Gastrointestinal: anorexia, nausea.

Incidence of <1% of Injections
Local reaction at injection site: hematoma.
Dermatologic: pruritus, rash, urticaria.
Respiratory: pharyngitis, other upper respiratory tract infections.
Gastrointestinal: abdominal pain, diarrhea, dysgeusia, vomiting.
Musculoskeletal: arthralgia, elevation of creatinine phosphokinase, myalgia.
Hematologic: lymphadenopathy.
Central Nervous System: hypertonic episode, insomnia,

photophobia, vertigo.

Additional safety data were gleaned from the field efficacy trial, in which 19,667 school children were immunized with Havrix™. In a subset, special local and general reaction data were solicited. The most commonly reported adverse events following administration of Havrix™ were injection-site pain (9.5%) and tenderness (8.1%), which were reported following first doses of Havrix™. Other adverse events were infrequent and comparable to the control vaccine Engerix-B® (Hepatitis B Vaccine, Recombinant, administered to a similar number of children). Additionally, no serious adverse events due to the vaccine occurred.

Postmarketing Reports

While no causal relationship has been established, rare voluntary reports of adverse events in people receiving Havrix™ that have been reported since market introduction of the vaccine include the following:

Local Reactions at Injection Site: localized edema.
Body as a Whole: anaphylaxis/anaphylactoid reactions, somnolence.
Cardiovascular: syncope.
Hepatobiliary: jaundice, hepatitis.
Dermatologic: erythema multiforme, hyperhydrosis, angioedema.
Respiratory: dyspnea.
Hematologic: lymphadenopathy.
Central Nervous System: convulsions, encephalopathy, dizziness, neuropathy, myelitis, paresthesia, Guillain-Barré syndrome, multiple sclerosis.
Other: congenital abnormality.

F. In conclusion, the vaccine has been thoroughly evaluated clinically and the data support its routine use in the prophylaxis against hepatitis A in adults and children two years of age and older. The package insert adequately reflects the results of the clinical evaluation of Havrix™.

VI Advisory Panel Consideration

Data regarding the manufacture, safety and efficacy of Havrix™ were discussed at the January 28, 1994 Vaccines and Related Biological Products Advisory Committee meeting.

VII Approved Package Insert

A copy of the approved package insert is attached.

Lewis J. Markoff, M.D., Chairman

TABLE 1

Characterization of the immune response

Primary course of vaccination	Vaccine dosage (ELISA Units)	Neutralizing Abs one month after primary course of vaccination		ELISA Abs (mIU/mo) one month after primary course of vaccination	
		% seroc.	GMT	% seroc.	GMT
In adults:					
2 doses, interval 1 mo.					
study HA 108	720	96.7	155	-	-
HA109	720	95.6	186	100	606
HA109	720	100	141	100	584
1 dose study HA104	1440	94.1	105	97.1	581.5
HA112	1440	100	>169.6	100	436.6
In children:					
2 doses, interval 1 mo.	360	-	-	100	483

TABLE 2

List of preclinical studies

Animal species	Objective	Results
Mice	Mouse potency test for stability studies and for lot release	Reproducible mouse potency test
	Effect of inactivation on immunity	Inactivated and non inactivated preparations have similar immunogenicity
Guinea pigs	Sensitization test for [redacted]	No sensitization
Chimpanzees	Pathogenicity of Master Seed Virus	Attenuated for chimps
	Safety	No abnormality detected
	Protective efficacy of active immunization	Vaccinated animals are protected against hepatitis and infection with HAV
	Protective efficacy of passive immunization	Vaccine induced immunoglobulin is capable of passive immunoprophylaxis
Marmosets	Dose response protective study Oral challenge study	Animals that responded to vaccination are protected against hepatitis

TABLE 3 (a)

1440 EL.U - Adults

Study Number	Primary schedule (months)	Booster (month)	Dose Level (EL.U)	No. subjects in immuno. analysis
PILOT HA-102a	0	6	1440/2 ml	
	0,14d	6	720	
	0,1	6	720	
	0	6	720	282
HAV-072	0	6	720	111
	0	6	1440/2 ml	
	0,14	6	720	
	0,28	6	720	
	0,7,21	6	720	
HAV-096	0	6	2 x 720	55
			1440/2 ml	
HAV-106	0,1	6	720	282
	0	6	720	
			1440/2 ml	
			2 x 720	
PIVOTAL				
HAV-104	0	6	1440	129
HAV-107	0	6	1440	140
HAV-112	0	12	1440	181

TABLE 3 (b)

360 EL.U - Children

Study Number	Primary schedule (months)	Booster (month)	Dose Level (EL.U)	No. subjects in immuno. analysis
PIVOTAL				
HAV-0052	0,1	6	360	26
HAV-066	0,1	6	360	239
HAV-084	0,1	6	360	190
HAV-085	0,1	12	360	239
HAV-088	0,1	6	360	99
HAV-089	0,1	6	360	91
SUPPORTIVE				
HAV-068	0,1	6	360	

PROTECTIVE EFFICACY - Children

Study Number	Country	Primary schedule (months)	Booster (month)	Dose Level (EL.U)	No. subjects in analysis
HAV-085	Thailand	0,1	12	360	40,119

TABLE 3 (c)

720 EL.U - Adults

Study Number	Primary schedule (months)	Booster (month)	Dose Level (EL.U)	No. subjects in immuno. analysis
PILOT				
HA-101	0,1	6	360	11
HA-102	0,1	6	360	388
HAV-003	0,1	2	180-720	199
HAV-011	0,1	2	720	52
HAV-013	0,1	2	720	93
	0,1	6	720	
HAV-018	0, 1, 2	12	720	36
PIVOTAL				
HAV-108	0,1	2/12	720	101
HA-109	0,1	6/12	720	159
HA-111	0,1	2/6/12	720	94
HA-112	0,1	2/6/12	720	40
	0,2	4	720	
HA-113	0,1	6	360/720/1440	40
HAV-108	0,1	2/12	720	101
HAV-016	0,1	2	720	229
HAV-023	0,14d	6	720	101
HAV-030	0,1	6	720	64
HAV-032	0,1	2/6	720	105
HAV-046	0,1	6	720	56
HAV-047	0,1	6	720	50
HAV-048	0,1	2/6/12	720	168
HAV-054	0,1	6	720	55
HAV-057	0,1	6	720	200
HAV-058	0,1	6	720	115
HAV-061	0,1	6	720	212
HAV-065	0,1	6	720	100
HAV-067	0,1	6	720	55
HAV-079	0,1	2	720	66
HAV-080	0,14d	10	720	549
SUPPORTIVE				
HAV-015	0,1	12	720 (1 mg Al)	62
HAV-040	0,14d	12	360/720	167
	0,28d			
	0,14d,28d			

TABLE 4

Numbers of subjects enrolled and included in analyses of reactogenicity and immunogenicity.

Studies	Numbers enrolled in pivotal studies	No. of subjects included in analysis of reactogenicity [a]	No. of Subjects included in analysis of immunogenicity [b]
1440 EL.U. primary dose	494	494	450
1440 EL.U. with booster	289[c]	264	261
720 EL.U.	2125	2125	1081[d]
360 EL.U.	1094	1021	524[e]
360 EL.U.*	40119**	1500	239

Note: Figures indicate subjects enrolled in non-US trials.

a Numbers of subjects returning evaluable checklists for analysis of reactogenicity

b Subjects were excluded from analysis of immunogenicity for reasons such as exceeding the time intervals set for between vaccinations and blood samplings; not conforming to inclusion/exclusion criteria e.g. exceeding the age range, initial seropositivity for anti-HAV antibodies, etc.

c 300 subjects enrolled in the two studies where a booster was administered at month 6, of these, 289 received the booster dose.

d Although 2125 subjects were included in an analysis of immunogenicity, 1081 of these subjects received vaccine according to a primary vaccination schedule of 0, 1 month with a booster at either month 2, 6 or 12

e Subjects from one study

* Protective efficacy study:subsets of the total enrollment were chosen randomly for analysis of reactogenicity and immunogenicity

** Total number randomized to receive either Havrix™ or Engerix®-B

TABLE 5a

Overall analysis of immunogenicity following primary vaccination (1440 EL.U.)

Timing	Number of subjects tested	Number of seropositive subjects	%	95% CI	GMT mIU/mL	95% CI (GMT)
Pre	450	0	0.0			
PI(d15)	444	391	88.1	84.6-90.9	293	270-317
PI(m1)	439	434	98.9	97.3-99.6	466	429-506
PI(m6)	417	395	94.7	92.0-96.6	208	192-225

Notes: Pre = prevaccination blood sample
PI(d15), etc = post-vaccination I blood sample at day 15, etc.
95% CI = 95% Confidence Interval

TABLE 5b

Overall analysis of immunogenicity in adults following booster dose (1440 EL.U.)

Timing	Number of subjects tested	Number of sero-positive subjects	%	95% CI (%)	GMT mIU/mL	95% CI (GMT)
PI(m6)	261	243	93.1	89.1-95.7	189	172-208
PII(m7)	253	253	100.0	98.1-100	4383	3908-4914

Notes: Pre = prevaccination blood sample
PI(d15), etc = post-vaccination I blood sample at day 15, etc.
95% CI = 95% Confidence Interval

The corresponding neutralizing antibody titers (% seropositive) at months 6 and 7 in HAV-104 were >179.5 mIU/mL (97.0%) and >3364 mIU/mL (100%) respectively

Table 6

Overall immunogenicity in children following vaccination[a]

Seroconversion / seropositivity rates and geometric mean titers of Anti-HAV antibodies at months					
	1	**2**	**6**	**7**	**12**
SC	498 / 522[b]	423 / 423[c]	212 / 212[d]	211 / 211[e]	105 / 105[b]
(%)	(95.4)	(100)	(100)	(100)	(100)
(95 % CI)	(93.1 - 97.0)	(98.8 - 100)	(97.8 - 100)	(97.8 - 100)	(95.6 - 100)
GMT	179	483	308	3831	1069
(95 % CI)	(169 - 190)	(446 - 522)	(280 - 340)	(419 - 4293)	(904 - 1264)

Notes:

a This table includes subjects from studies HAV-052, HAV-066, HAV-084, HAV-088 and HAV-089.
b Only includes results of HAV-066.