

paring Vaqta and another inactivated hepatitis A vaccine, Havrix, in a Jewish religious community in Monroe, NY, having experienced hepatitis A outbreaks. In this study in children and adolescents, Vaqta demonstrated 100% onset of protection after the primary dose, with long-term (6 years) protection against illness following a booster dose.

**Medical:** Vaqta is administered by intramuscular injection with a standard adult dosage of 1.0 mL (50 U) and pediatric dosage of 0.5 mL (25 U), with a booster of the same dosage at 6-18 months.

**Market:** Vaqta competes directly with Havrix from GlaxoSmithKline. A major advantage for Vaqta vs. Havrix is that only two doses of Vaqta are required for children, while three are required with Havrix.

The 2004 Average Wholesale Price (AWP) for Vaqta Pediatric is \$39.23/single-dose vial, with a Direct Cost (DC; manufacturer's discount) of \$31.38; \$39.23/single-dose prefilled syringe, with DC of \$31.38; \$185.11 for five syringes, with DC of \$148.09; and \$370.24 for 10 prefilled syringes, with DC of \$297.19. The AWP for Vaqta (adult) is \$78.45/single-dose vial, with DC of \$62.76; \$370.24 for five, with DC of \$296.19; \$78.45/single-dose prefilled syringe, with DC of \$62.76; \$370.24 for five, with DC of \$296.19; and \$717.76 for 10 prefilled syringes, with DC of \$593.13 (*Red Book*, 2004).

As reported by the National Immunization Program (NIP), Centers for Disease Control and Prevention (CDC) (4/2005), the average private-sector cost per dose is \$30.37 for a package of 10 single dose vials. The cost negotiated by NIP, CDC, for bulk contract purchase for public-sector state and local immunization programs is \$12.15/dose per package of 10 single dose vials. These prices include the \$.75/dose (\$.75/covered component vaccine) Federal Excise Tax charged by the manufacturer for the federal vaccine injury compensation program. Merck's contract with NIP, CDC, expires on March 31, 2006.

In April 2005, the U.K. National Health Service (NHS) cost was reported to be £15.65 (~\$29.97) for Vaqta Paediatric vaccine

In its April 18, 2005 price list, FFF Enterprises, a major biologics distributor, reported \$69.73/single-dose 50 U 1 mL vial (\$34.86 in March 2004) and \$329.10/5 single-dose 1 mL vials. In March 2004, FFF reported \$34.86/single-dose 25 U 0.5 mL vial; \$69.73/single-dose 50 U 0.5 mL vial; and \$329.10/package of five single-dose 50 U 0.5 mL vials (\$65.82/dose).

## 412 Hepatitis A Virus Vaccine/GSK

### Hepatitis A Virus Vaccine, Inactivated - Havrix

**Status:** approved; marketed

#### Organizations Involved:

GlaxoSmithKline Biologicals S.A. – Manuf.

GlaxoSmithKline Inc. – USA Mark.

SmithKline Biologicals S.A. – R&D; Tech.; Former inv.  
National Institute of Allergy and Infectious Diseases (NIAID), NIH – R&D; Tech.

National Institutes of Health (NIH) – Parent org.

Walter Reed Army Institute of Research (WRAIR),  
U.S. Army – R&D

National Institute of Biological Standards and Control (NIBSC) – R&D

China National Biological Products Corp. – Manuf.  
other; Asia mark.

Shanghai Institute of Biological Products – Manuf.  
other; Asia mark.

**Cross ref:** See the Hepatitis A Vaccine Products entry (#410) and the entry for the other marketed hepatitis A vaccine, Vaqta (#411) Vaqta from Merck & Co. See also Twinrix (#415), a combination hepatitis A and B virus vaccine containing Havrix as a component.

**Description:** Havrix is an aqueous formulation of whole inactivated hepatitis A virus (strain HM-175). The vaccine is prepared from virus cultured in MRC-5 human diploid cells, inactivated with formaldehyde, and adsorbed onto aluminum hydroxide adjuvant.

The standard used to express viral antigen activity for Havrix is derived from the "enzyme linked immunosorbent assay" or ELISA, with results reported in, "ELISA Units", or EL.U. One ELISA Unit is equivalent to about 0.42 ng of hepatitis A virus (HAV) viral protein. ELISA Units measurements generally correlate with the presence of antigenic epitopes and the in vivo induction of neutralizing antibodies. This assay is not used with the other hepatitis A vaccine, Vaqta.

The vaccine is supplied in vials or prefilled disposable syringes. After recommended thorough agitation (shaking) prior to use, Havrix is a turbid white suspension. Havrix is/was packaged as: a) pediatric dosage of 360 EL.U. hepatitis A virus antigen in 0.5 mL solution single-dose vials (phased out in late 1990s); b) 720 EL.U. of hepatitis A virus antigen in 0.5 mL solution in single-dose vials and prefilled syringes (pediatric dosage); and c) 1,440 EL.U. of hepatitis A virus antigen in 1 mL solution in single-dose vials and prefilled syringes (adult dosage). Each 1 mL of adult dosage vaccine contains at least 1,440 EL.U. of viral antigen adsorbed on 0.5 mg of aluminum (as aluminum hydroxide). Havrix formulations also contain 0.5% (weight/volume) of 2-phenoxyethanol as a preservative. Other excipients present in the vaccine are

amino acid supplement (0.3% w/v) in a phosphate-buffered saline solution, and polysorbate 20 (Tween 20; 0.05 mg/mL). The vaccine also contains not more than 5 µg per adult dose of residual MRC-5 human cellular proteins, and traces of not more than 0.1 mg/mL of formalin (formaldehyde). Each 720 EL.U. of hepatitis A virus antigen contains not more than 2.5 µg total proteins, including about 100 ng of viral antigen and 1 ng of bovine serum albumin. The vaccine is stored at 2-8°C (refrigerated) and has a shelf life of 2 years.

With its 2001 approval, pediatric doses of Havrix are also packaged in pre-filled Safety Tip-Lok syringes incorporating BD SafetyGlide Needles from Becton Dickinson and Co. [in compliance with revised Occupational Safety and Health Administration (OSHA) standards for blood-borne pathogen exposure].

**Nomenclature:** Hepatitis A Virus Vaccine/GSK [BIO]; Havrix [TR]; Hepatitis A Virus Vaccine, Inactivated [FDA]; HAVsorbat SSW [TR foreign]; HAV [SY CDC]

**History:** Hepatitis A virus (HAV) strain HM-175 (or HM175) was originally isolated from a fecal sample obtained from a stricken patient during an outbreak near Melbourne, Australia, in 1976. The H stands for hepatitis, M stands for the name of the electron microscopist involved, and 175 was the laboratory accession number. Culture and isolation of strain HM-175 in African green monkey primary kidney cells were reported in 1981.

HAV strain HM-175 was subsequently adapted to grow in human diploid MRC-5 cells and was attenuated, resulting in decreased pathogenicity, by serial passage (multiple reculturing of the virus). The host MRC-5 cell line was originally developed by the National Institute of Biological Standards and Control (U.K.). This provided the virus stock used for vaccine development and production. The adaptation of strain HM-175 to MRC-5 cells (by NIAID, NIH; discussed below) increased the antigen yield and the rate of viral replication. The MRC-5 cell line meets World Health Organization (WHO), FDA, and other countries' requirements for continuous cell lines for production of human vaccines. MRC-5 is considered by many to be the best characterized and safest cell line for production of vaccines. The cell line is free of contamination (e.g., detectable viruses), shows normal karyology, and is not tumorigenic. MRC-5 has been used for over 25 years for production of various live and inactivated vaccines, and there have been no reports of hypersensitivity due to residual MRC-5 proteins in Havrix or other viral vaccines cultured in MRC-5 cells. [Note, according to FDA, "Products that are manufactured in genetically unmodified MRC-5 or WI-38 cells do not need characterization of these cell substrates by karyology or tumorigenicity, since extensive characterization has already been performed and published for these cell lines."].

Sequencing of strain HAV HM-175, both wild and culture-adapted virus, has shown that attenuation depends on a limited number of nucleotide changes (mutations) distributed throughout the viral genome. Strain HM-175 has also been used extensively for production of murine monoclonal antibodies used extensively as hepatitis A virus reference reagents. A serially passaged live hepatitis A virus HM-175 strain vaccine was reported in 1992 to be avirulent in healthy volunteers.

Both the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH; Bethesda, MD), and the U.S. Army played major roles in the development of Havrix. Strain HM-175 and inactivated vaccines were originally developed by NIAID researchers. Clinical trials were conducted by NIAID, NIH, and the U.S. Army with assistance from the Centers for Disease Control and Prevention (CDC). See the "Technology transfer" and "Clinical Trials" sections for further information about the involvement of these organizations.

**Companies:** Havrix was commercially developed and originally manufactured by SmithKline Beecham S.A. (Rixensart, Belgium), CBER/FDA est. no. 1090, now GlaxoSmithKline Biologicals S.A., est. no. 1617, a subsidiary of GlaxoSmithKline plc (GSK). SmithKline Beecham plc (SKB) and Glaxo Wellcome plc merged in Dec. 2000 to form GlaxoSmithKline plc. Havrix is marketed in the U.S. by GlaxoSmithKline Inc., and internationally by GSK affiliates. Havrix is available in over 50 countries.

SmithKline Beecham Biologicals (now GSK) concluded an agreement in 1994 with the China National Biological Products Corp. and the Shanghai Institute of Biological Products for the manufacture and marketing of Havrix in the Peoples Republic of China (PRC). All three parties invested in a joint venture located in Shanghai. [Hepatitis A is a major public health problem in China. Over 292,000 cases were reported in one outbreak alone in Shanghai].

**Manufacture:** Havrix is produced by a relatively simple and well-understood process similar in many respects to production of inactivated poliovirus vaccine (IPV). Host MRC-5 human diploid cells are tested to ensure the absence of viruses and other contaminants. The cells are cultured to form a cell layer and seed virus (hepatitis A virus strain HM-175) is added. The virus is incubated for three weeks and replicates in the host cells without killing them. The cell culture is washed to remove medium components and the remaining cells are lysed (fractured by freezing and thawing) to form a suspension.

HAV virions are purified in several steps including sterile filtration, ultrafiltration, and concentration by column chromatography. These steps remove lipids, proteins, and other cellular material. Purified lysates are pooled and

treated with formalin (formaldehyde), a powerful reducing agent, at a concentration of 250 µg/ml at 37°C for 15 days. Formalin is a solution of about 37% by weight of formaldehyde gas in water (usually with 10-15% methanol to prevent polymerization). Formalin inactivation provides a sterile suspension of inactivated virus. This is adsorbed onto aluminum hydroxide adjuvant, and 2,5-phenoxyethanol at a concentration of 5 mg/ml is added as a preservative.

Tests have been developed, validated and are used to demonstrate the purity of the cell substrate used for each production cycle, the quality of virus harvested, the adequacy of the purification and inactivation processes, and conformity to specifications for purity, safety and potency. After passing all tests, the formulated vaccine is filled in sterile vials.

The period of time (3 weeks) during which purified viral lysates are treated with formalin is estimated to be about three-times the period required to reduce infectious virus titer below detectable levels using standard viral titration procedures in MRC-5 host cells. The sensitivity of the MRC-5 cell culture test for residual live virus has been shown to be far superior to inoculation of susceptible nonhuman primates.

Hepatitis A virus antigen content of the bulk vaccine is determined before alum adsorption. The immunogenicity of the final vaccine is evaluated using a mouse potency test in which mice are injected with graded doses of vaccine, blood samples are taken over a four week period, and the proportion of seroconverted mice at each dilution is used to determine the median effective dose (ED<sub>50</sub>). All vaccine production lots have to pass specifications developed on the basis of consistency lots (which were also found to be acceptable in all respects in clinical trials). The reference vaccine used for comparison is one of these consistency lots. Vaccine stability is determined using the same mouse potency test. Vaccine lots stored for over 24 months still meet the specifications for release of new vaccine lots. Accelerated stability tests are carried out on vaccine lots at time of release and on vaccine lots stored for 15 months at -2°C to -8°C. Accelerated stability testing involves storing lots of vaccine at 37°C for 1, 2 and 3 weeks.

Final vaccine lots are tested and characterized following general requirements for biologics including: description of the physical aspects of the vaccine, identity, volume, pH, sterility, and general safety. Aluminum and 2-phenoxyethanol contents are quantified. Endotoxin content is assayed using the *Limulus* amoebocyte lysate (LAL) test, and has been found to consistently be less than one endotoxin unit per dose. Final vaccine lots do not contain detectable bovine albumin or immunoglobulin (from cell culture media) using ELISA assays capable of detecting 1

ng of these proteins. MRC-5 host cell proteins are also undetectable in the vaccine using antibody-based assays. Havrix contains no human blood or plasma-derived components.

The particulate nature of the hepatitis A virus is preserved throughout manufacture. Electron micrographs of the vaccine show viral particles with a mean diameter of ~27 nm. Viral proteins (antigens) can be identified by immunoblots using hepatitis A virus whole capsid and hepatitis A virus VP0, VP1 and Px proteins. Antigenicity can be confirmed by routine immunological assays (ELISA and RIA).

**FDA class:** Biologic PLA

**CBER class:** Viral And Rickettsial Vaccines

**Approvals:** Date = 19950222; first approval, PLA ref. no. 92-0465 and ELA supplement no. 92-0464; Indication = for active immunization of persons 2 years of age or older against disease caused by hepatitis A virus

Date = 19960526; PLA supplement ref. no. 95-0877; Indication = approval of a more concentrated pediatric dosage formulation, and a new pediatric vaccination schedule, i.e., 720 E.I.U/0.5 mL at 0 and 6-12 months

Date = 19970627; PLA supplement; Indication = for prevention of hepatitis A in persons with chronic liver disease

Date = 20010700 (est.); BLA supplement; Indication = approval of prefilled Safety Tip-Lok syringes from Becton Dickinson and Co.

**Indications:** [portions of the "INDICATION AND USAGE" section from product insert/labeling]:

Havrix is indicated for active immunization of persons ≥ 2 years of age against disease caused by hepatitis A virus (HAV). Immunization with Havrix is indicated for those people desiring protection against hepatitis A. Primary immunization should be completed by at least 2 weeks prior to expected exposure to HAV. Individuals who or, or will be, at increased risk of infection by HAV include...Travelers...Military personnel... People living in, or relocated to, area of high endemicity...People with chronic liver disease...Others: Persons engaging in high-risk sexual activity (such as men having sex with men); Residents of a community experiencing an outbreak of hepatitis A; Users of illicit injectable drugs; Persons who have clotting-factor disorders (hemophiliacs and other recipients of therapeutic blood products)...

**Status:** The original PLA was filed on Dec. 22, 1994, and granted in March 1995; review time = ~1.06 years. The first approval for Havrix was in Switzerland in 1991. The vaccine has subsequently been approved in most countries worldwide.

The Vaccines and Related Biological Products Advisory Committee, FDA, had reviewed Havrix and recommended approval of Havrix over one year before its

approval by FDA. At the time, Havrix had already been approved and marketed in over 25 countries (including the U.K., France, Italy, Germany and Switzerland), and over 4 million doses of Havrix had been sold worldwide. Havrix (along with Varivax) has been cited by some critics of FDA as an example of a product for which FDA needlessly delayed approval.

A new, more concentrated pediatric dosage and vaccination schedule (going from 3 to 2 injections) for Havrix was approved on June 26, 1996. This reduced the total cost and increased convenience and compliance. An initial dosage of 720 U/0.5 mL of Havrix is now recognized as providing protection in children and adolescents 2-18 years old for about one year, and a single booster is recommended at 6-12 months if extended protection is needed. Previously, children and adolescents were recommended to receive two 360 U/0.5 mL doses of Havrix at zero and one month, followed by a booster at 6-12 months. This dosage schedule closely matches that of the other approved hepatitis A virus vaccine, Vaqta. The 360 U/0.5 mL dosage was phased out after this approval.

Supplementary approval was granted in July 1997 for prevention of hepatitis A virus infection in persons with chronic liver disease, including alcoholic cirrhosis, chronic hepatitis B, chronic hepatitis C, autoimmune hepatitis and primary biliary cirrhosis. To be considered chronic, liver inflammation must generally be present for at least six months. Havrix is the only vaccine approved for immunization against hepatitis A in chronic liver disease patients.

CBER/FDA reported in Dec. 2000 that Havrix was being manufactured by GSK using bovine-derived materials from countries on the official USDA list of countries known to have cattle with BSE. See the Regulatory section of the Vaccine Products entry (#342) for further information about bovine source materials and bovine spongiform encephalopathy (BSE). In March 2004, CBER/FDA again reported that Havrix was one of five vaccines on its "Current list of vaccines using bovine-derived materials from countries on the USDA's BSE list." CBER/FDA also reported that "there is no evidence that any case of vCJD [variant Creutzfeld-Jakob disease in humans] has been caused by or is related to vaccines manufactured with bovine-derived materials obtained from countries in which BSE or a significant risk of BSE exists (i.e., countries on the USDA list), and thus the risk of vCJD is theoretical."

Havrix is not a universal/required vaccine, and is not included in the national vaccine liability insurance program

**Tech. transfer:** U.S. government laboratories played a significant role in the discovery, development, and testing of Havrix. SmithKline Beecham (SKB), now Glaxo-

SmithKline, has licensed key inventions from the National Institutes of Health (NIH; Bethesda, MD). The National Institute of Allergy and Infectious Diseases (NIAID, NIH), U.S. Army, and the Centers for Disease Control and Prevention (CDC) were significantly involved in the development and clinical testing of the vaccine, with much of this conducted through formal Collaborative Research and Development Agreements (CRADAs) with SKB (GSK). CRADAs allow private sector monetary and other support and participation in federal research, development and testing activities, and the exclusive licensing of resulting inventions.

Federal labs participated in the development of Havrix through CRADAs with SKB that began in Nov. 1988. These CRADAs encompassed many aspects of the vaccine's development, from preclinical studies through large-scale clinical trials. Preclinical studies and Phase I and other clinical trials with Havrix were conducted by Dr. R. Purcell and coworkers, NIAID, NIH, through CRADAs with SKB. The Walter Reed Army Institute of Research (WRAIR; Washington, DC), U.S. Army, entered into a CRADA with SKB in 1991. This involved the Army conducting (with assistance from CDC) clinical trials, including large-scale clinical efficacy trials in Thailand in over 40,000 children.

SKB, now GSK, has nonexclusively licensed various patent properties from NIH; related to the isolation of hepatitis strain HM-175, methods for its cell culture and attenuation, and inactivated HM-175 strain vaccines. These inventions represent the contributions of Dr. R.H. Purcell, his co-workers within NIAID, and collaborators. Because SKB nonexclusively licensed these inventions, it was exempt from NIH requirements (then in force, never used, subsequently abandoned) that required "reasonable pricing" of inventions exclusively licensed from NIH. Culture collection deposits of hepatitis A virus strain HM-175 associated with licensed NIH patents include American Type Culture Collection (ATCC) VR 2089, VR 2090, VR 2091, VR 2092 and VR 2093.

Patents assigned to NIH, licensed by SKB/GSK include:

- a) U.S. 4,532,215, "Isolation of Hepatitis A Virus Strain HM-175," by Daemer, R.J.; Feinstone, S.M.; Gust, I.D.; Purcell, R.H.; issued on July 30, 1985. This was the first U.S. patent concerning the isolation of hepatitis A virus strain HM-175 from Australian stool samples and its continuous culture and attenuation in primary African green monkey kidney (AGMK) cell cultures. Previously, marmosets were the major source for growth of hepatitis A virus and production of hepatitis A antigens.
- b) U.S. 4,636,469, "Isolation of Hepatitis A Virus Strain HM-175," by Daemer, R.J.; Feinstone, S.M.; Gust, I.D.; Purcell, R.H.; issued on Jan. 13, 1987.
- c) U.S. patent 4,620,978, "Hepa-

titis A Virus Purified and Triply Cloned," Nov. 4, 1986. This includes methods for preparation of master seed lots of hepatitis A virus HM-175 strain for vaccine production in primary African green monkey kidney (AGMK) cell cultures. d) U.S. 4,894,228, "Vaccine Against Hepatitis A Virus," Jan. 16, 1990. This patent concerns attenuated hepatitis A virus strain HM-175 Pass 35 and clones of this virus useful for production of hepatitis A vaccines. The complete nucleotide sequence of strain HM-175 Pass 35 is provided. e) U.S. 6,180,110, "Attenuated hepatitis A virus vaccine which grows in MRC-5 cells," Jan. 2001, substantively covering Havrix. SKB/GSK has also licensed various foreign equivalents of these U.S. patents. [Note, co-inventor Dr. I.D. Gust was affiliated with the Commonwealth Serum Labs., Ltd. (now CSL Ltd.). It is unknown whether CSL receives royalties from NIH's licensing of HAV HM-175.]

**Trials:** Clinical studies began in Dec. 1998. The original PLA included 43 studies involving more than 26,000 persons conducted as part of SKB's development plan and post-marketing experience. Trials included immunogenicity studies in adults and pediatric populations in which induction of hepatitis A virus-specific antibodies was used as a surrogate marker for clinical efficacy (prophylaxis against natural infection), field trials in which actual prophylactic efficacy was determined, and field studies in communities with ongoing outbreaks of hepatitis A virus infection in which the vaccine provided protection and slowed the course of the epidemic.

In three immunogenicity studies involving 400 healthy adults administered a single 1,440 EL.U. dose of Havrix, virus-specific humoral antibodies (seroconversion; primarily IgG antibodies) were detected in over 96% one month after vaccination. Seroconversion was determined by induction of at least 20 mIU/ml of hepatitis A virus antibody, the lower limit of available antibody assays. Geometric mean titers (GMTs) of seroconverters ranged from 335 to 637 mIU/ml at one month. GMTs following a single dose of Havrix were at least several times those provided by administration of immune globulin.

The Walter Reed Army Institute of Research (WRAIR; Washington, DC), U.S. Army, conducted a pivotal, large-scale, Phase III trial in Thailand that substantiated the protective efficacy of Havrix. This was a controlled trial in 40,119 high-risk children (ages 1-16) receiving either Havrix or Engerix-B (hepatitis B vaccine). Children randomly received Havrix (360 EL.U.) or Engerix-B at 0, 1 and 12 months. Havrix provided over 94% protection against disease (95% confidence intervals between 74-98%). In outbreaks investigated during the trial, 26 clinical cases were noted with none involving Havrix recipients. Subsequent to completion of the trial, up to three additional cases of very mild hepatitis A virus infection may have

occurred in Havrix recipients. Including these cases, the calculated efficacy for prevention of infection in this high risk population would be 84% (95% confidence intervals 60-94%).

**Medical:** Havrix induces Geometric Mean Titers (GMTs) of hepatitis A virus-specific antibodies in seroconverters comparable to those in persons having experienced natural infection with hepatitis A virus, and at least several times higher than those provided by administration of immune globulin.

Adults receive primary immunization with a single intramuscular injection of 1,440 EL.U. in 1 mL, followed by another dosage of 1,440 EL.U. in 1 mL six to 12 months later to assure long-term immunity. Primary immunization should occur at least two weeks before any expected/potential exposure to HAV. For those requiring both immediate and long-term protection, Havrix may be administered along with immune globulin. Children and adolescents (2-18 years of age) may follow one of two approved schedules: a primary course of two doses, 360 EL.U./0.5 mL each, given at 0 and 1 month (one month apart), with a booster of 360 EL.U./0.5 mL 6 to 12 months after initiation of the primary course; or a newer regimen involving a primary course with a single dose, 720 EL.U./0.5 mL, at month 0, with a 720 EL.U./0.5 mL booster 6 to 12 months after initiation of the primary course.

**Market:** The 2004 Average Wholesale Price (AWP) for Havrix (adult) is \$65.50/single-dose vial; \$65.08 for pre-filled single-dose syringe, and \$325.40 for five (*Red Book*, 2004). The AWP for Havrix Pediatric is \$33.46/single-dose vial, \$159.97 for five, \$319.96 for 10, and \$799.88 for 25. The AWP for Havrix Pediatric with SafetyGlide pre-filled syringe is \$784.16 for 25 (either 23 or 25 gauge needle).

As reported by the National Immunization Program (NIP), Centers for Disease Control and Prevention (CDC) (4/2005), the average private-sector cost per dose is \$56.17 for single dose vial; \$54.98 for single dose pre-filled syringe, including in packages of 10. The cost negotiated by NIP, CDC, for bulk contract purchase for public-sector state and local immunization programs is \$18.50/dose for all presentations (vials and pre-filled syringes). These prices include the \$.75/dose (\$.75/covered component vaccine) Federal Excise Tax charged by the manufacturer for the federal vaccine injury compensation program. GSKs contract with NIP, CDC, expires on June 30, 2005.

In April 2005, the U.K. National Health Service (NHS) cost was reported to be £23.81 (~\$45.60) for Havrix Monodose (adult) and £18.03 (~\$34.50) for Havrix Junior Monodose (pediatric).

Worldwide sales of Havrix were \$370.6 million in 1997.

Havrix competes directly with Hepatitis A Vaccine,

Inactivated (Vaqta) from Merck & Co. Both Havrix and Vaqta are inactivated hepatitis A virus vaccines and have shown high (95 to 100%) levels of protection from hepatitis A infection in clinical trials. Unlike Havrix, Vaqta is formulated without a preservative. Twinrix (from GSK), a combination vaccine containing Havrix and recombinant hepatitis B vaccine (Engerix B also from GSK), indirectly competes with Havrix.

## 413 Hepatitis A Virus Vaccine/ Berna

**Hepatitis A Virus Vaccine, Inactivated - Epaxal Berna**  
**Status:** marketed in European and other countries, not in U.S.

### Organizations Involved:

Berna Biotech Ltd. – Manuf.; R&D; Tech.; Europe mark.; Intl. mark.

Acambis plc – Parent

Swiss Serum and Vaccine Institute Berne – R&D; Tech.; Former

**Cross ref.:** See the entry above for Hepatitis B Vaccine Products. See also the other hepatitis A virus vaccine entries.

**Description:** Epaxal is an aqueous virosomal (liposomal) formulation of formalin (formaldehyde)-inactivated whole cell hepatitis A virus (HAV) RG-SB strain cultivated on MRC-5 human diploid cells adsorbed to immunopotentiating reconstituted influenza virosomes (cell membrane-like phospholipid structures) along with two influenza virus antigens anchored in the membrane – hemagglutinin (HA) and neuraminidase (NA). Each 0.5 mL dose contains at least 500 radioimmunoassay units of HAV antigen along with phospholipids, 350 mg; influenza A virus hemagglutinin, 5-16 µg; formaldehyde, <25 µg; and sodium chloride, 0.85-0.95% (w/v). The vaccine is stored at 2-8°C (refrigerated). The vaccine is supplied in packages of one or 10 single-dose, pre-filled syringes.

Epaxal does not contain thiomersal (mercury-based preservative) and is the only aluminum-free hepatitis A vaccine worldwide, i.e., it does not contain any aluminum-based adjuvant. Epaxal also contains no antibiotics and no preservatives.

Although not marketed in the U.S., virosomal vaccines (without adjuvant) are a proven technology. Besides Epaxal, Berna Biotech currently manufactures and markets Inflexal V, an intramuscular injected influenza virus subunit vaccine, primarily marketed in Switzerland and other European countries (see related entry). Sanofi manufactures and markets Inivac, a cell cultured virosomal influenza vaccine (see related entry).

**Nomenclature:** Hepatitis A Virus Vaccine/Berna [BIO]; Hepatitis A Virus Vaccine Inactivated [FDA, if approved

in U.S.]; Epaxal Berna [TR foreign]

**Biological:** Virosomes are liposomes, artificial (phospho)lipid bilayer membranes resembling the cell membrane, that carry purified two influenza virus antigens anchored in their membrane – hemagglutinin (HA) and neuraminidase (NA) – which enable the virosomes to fuse with cells of the immune system. . Virosomes are composed of a completely biodegradable mixture of synthetic and natural phospholipids forming a liposome membrane. The virosomes, with influenza virus NA and HA, function as adjuvants as well as the delivery system for the hepatitis A antigens. The virosomes form liposomal globules about 150 nm in size with influenza HA and NA on their surface, in addition to membrane-derived phospholipids, which enable the virosomes to fuse (via the endolysosomal pathway) to immune cells and deliver their contents. After endocytosis uptake into the cell, the viral HA mediates membrane fusion with endosomes, much the same as by influenza virus, releasing the virosome contents into the cytoplasm. The virosomes then degrade within cells. Virosomes mimic the natural method of antigen presentation and uptake of influenza virus, with antigens presented on the surface of lipid-based membranes (like cell membranes). Virosomal vaccines, including Epaxal, induce both T-cell (cellular) and B-cell (humoral) immune responses.

**Companies:** Epaxal was originally developed Swiss Serum and Vaccine Institute Berne, now Berna Biotech Ltd., which was acquired by Acambis plc in Aug. 2003. The vaccine is manufactured and marketed in various European countries by Berna Biotech Ltd.

**Indications** [European]: active immunization against hepatitis A for adults and children after completion of the first year of age.

**Status:** Epaxal is approved in various individual European and other countries worldwide, but not in the U.S. It has not received European Union approval (probably because this was not needed with approvals in individual countries). Besides 14 European countries, it is marketed in Hong-Kong, Pakistan, Singapore, Latin America: Argentina, Chile, and Colombia.

**Trials:** After a single injection of Epaxal, 88% of healthy seronegative adults seroconverted (titers > 20 mIU/L) after 14 days and 98% after 1 month. Three to 12 months post-immunization, between 92-94% maintained protective antibody levels. One month after a booster dose, given approximately one year after primary immunization, 99.8% of vaccine recipients had high levels of protective antibody, with a 22-fold increase in geometric mean titer. Mathematical modelling suggests that >90% of vaccine recipients who receive primary immunization and a booster at 1 year will retain protection for at least 10 years.

A post-marketing safety study has shown that the in-

idence of local adverse reactions with Epaxal is much less than with Havrix.

**Medical:** The vaccine provides rapid, long lasting protection and exhibits very good tolerability. Since vaccine protection lasts at least 1 year, booster vaccination is only indicated if more than one year has passed since primary immunization. The booster vaccination induces very high antibody titers which presumably will confer protection for 5 to 10 years.

Besides its purity, including lack of thimerosal, aluminum and preservatives, Epaxal offer excellent local tolerability in both adults and children, with minimal allergic reactions; quick, efficient protection against hepatitis A infection (100 % protection after 10 days), making it useful for last minute travelers; a small injection volume (0.5 ml); and it can also be administered subcutaneously. Booster vaccination may be administered up to 5 years after the primary vaccination. Epaxal can be administered simultaneously with other vaccines.

**Tech. transfer:** The Swiss Serum and Vaccine Institute Berne, now Berna Biotech, developed virosomal vaccine technology and has received patents including U.S. 5,879,685, "Immunostimulating and immunopotentiating reconstituted influenza virosomes and vaccines containing them"

**Market:** In April 2005, the U.K. National Health Service (NHS) cost was reported to be £23.81. (~\$45.60), both for the Monodose (adult) and Havrix Junior Monodose (pediatric) doses.

## 414 Hepatitis A Virus Vaccine/ Sanofi

### Hepatitis A Virus Vaccine, Inactivated - Avaxim

**Status:** marketed in Europe and other countries, not U.S.

#### Organizations involved:

Sanofi Aventis S.A. – Manuf.; R&D; Tech.; Intl. mark.

Aventis Pasteur S.A. – Former

Sanofi Pasteur MSD - Europe mark.

Aventis Pasteur MSD – Former

**Cross ref.:** See the Hepatitis A Vaccine Products entry and the entries for the two U.S. marketed hepatitis A vaccines: Havrix, from SmithKline Beecham Biologicals S.A. and Vaqta from Merck & Co., Inc. See also Viatim (Vivaxim), a combination vaccine of which Avaxim is a component.

**Description:** Hepatitis A Virus Vaccine, Inactivated or Avaxim is an aqueous formulation of inactivated whole hepatitis A virus (HAV) prepared from attenuated hepatitis A virus GBM strain cultured in MRC-5 human diploid fibroblasts inactivated with formalin/formaldehyde and adsorbed onto aluminium hydroxide adjuvant.

Each 0.5 mL dose of Avaxim contains inactivated

hepatitis A virus, 160 AV antigen units (in the absence of an international standardized reference, using an in-house reference). Other constituents include aluminum hydroxide, 0.3 mg; 2-phenoxyethanol, 2.5 µg; formaldehyde, 12.5 µg; Hank's medium 199; water for injection; and neomycin, trace amounts. Hydrochloric acid or sodium hydroxide may be used to adjust the pH of the fluid content, i.e., Hanks medium 199 plus water for injection. Some sources, perhaps not as recent, report the vaccine contains traces of polysorbate 80 (Tween 80).

This vaccine is also a component of a bivalent vaccine. See the Viatim (Vivaxim) entry. This is also marketed primarily as a traveler's vaccine and combines protection from hepatitis A with protection from *Salmonella typhi* infection.

**Biological:** The HAV GBM strain was isolated in 1975 from a patient during an outbreak in Gomaringen, Germany, by B. Flehmig, Tübingen University. The virus was adapted and propagated by culture in primary human kidney cells, followed by adaptation in human diploid fibroblast cells and human diploid MRC-5 cells. The resulting culture-adapted virus showed some mutations, with these correlating with attenuation when inoculated into chimpanzees. GBM strain-derived vaccines have been shown immunogenic in guinea pigs, goats, mice and humans.

**Nomenclature:** Hepatitis A Virus Vaccine/Sanofi [BIO]; Hepatitis A Virus Vaccine, Inactivated [FDA, if it was approved in U.S.]; Avaxim [TR]

**Companies:** Avaxim is manufactured by Sanofi Aventis S.A. (formerly Aventis Pasteur S.A.) The vaccine is marketed in France and other European countries by Sanofi Pasteur MSD Ltd. (formerly Aventis Pasteur MSD), a joint venture of Sanofi Aventis S.A. and Merck & Co., Inc. The vaccine is marketed in other countries by Sanofi Aventis S.A. affiliates.

**Manufacture:** The virus is cultured, harvested by physical methods, further purified, inactivated with formalin (formaldehyde), and adsorbed onto aluminum hydroxide adjuvant. Apparently, after culture in MRC-5 fibroblasts cells using Hank's medium 199, inactivation with formalin/formaldehyde and purification, bulk vaccine is adjusted for antigen content according to prior results and the use of an in-house enzyme immunoassay in comparison with in-house reference materials. No international reference antigen preparation was available at that time of Avaxim development. Antigen is adsorbed to aluminium hydroxide, 2-phenoxyethanol is added as an antimicrobial preservative, and antigen concentration is adjusted using Hank's medium 199 and sterile water for injection. Potency is reported in European hepatitis A units (EAU).

**Medical:** Avaxim is administered by intramuscular (IM) injection. The primary vaccination involves a dose of vaccine, followed by a booster injection 6 to 12 months